Evaluation of patient adherence to artemether-lumefantrine obtained from public and private drug outlets in Tanzania

KATIA JOY BRUXVOORT

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Research group affiliation(s): IMPACT2

Declaration

I, Katia Joy Bruxvoort, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: 

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Abstract

Adherence to artemisinin-based combination therapies (ACTs) for malaria is important for effective treatment. This thesis compares adherence to ACTs obtained in the public and private retail sectors, describes an intervention to improve dispenser knowledge and patient adherence, and addresses challenges of measuring patient adherence to ACTs.

A cluster randomised trial of a text message intervention targeted at dispensers in Accredited Drug Dispensing Outlets (ADDOs) was conducted in Tanzania to improve provision of advice on artemether-lumefantrine (AL) and as a result patient adherence. An observational study was also conducted among patients obtaining AL from public health facilities. In a third study, smart blister packs that recorded when pills were removed were used to assess the validity of self-report. Adherence was measured as completion of all doses ("completed treatment") and completion of each dose at the correct time ("timely completion").

The intervention improved dispenser knowledge, but had no effect on patient completion of treatment (intervention 68.3%, control 69.8%, *p* [adjusted] = 0.6), or timely completion (intervention 33.1%, control 32.6%, *p* [adjusted] = 0.9). ADDO patients were wealthier, more educated, older, sought care later in the day, and were less likely to test positive for malaria than health facility patients. The adjusted odds of completed treatment and of timely completion for ADDO patients were 0.65 (95% CI: 0.43, 1.00) and 0.69 (95% CI: 0.47, 1.01) times that of health facility patients. Timely completion, but not completed treatment, was lower by smart blister packs than by self-report (37% vs. 24%, p<0.0001).

Adherence to AL in both sectors was suboptimal. As the private sector continues to be important for malaria treatment, better understanding is needed of which aspects of patient care are most important to maximise adherence and how methods of assessing adherence can be improved.

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Abbreviations

ACT	Artemisinin-based combination therapy
ADDO	Accredited Drug Dispensing Outlet
AL	Artemether-lumefantrine
AMFm	Affordable Medicines Facility- malaria
AQ	Amodiaquine
AS	Artesunate
ASAQ	Artesunate-amodiaquine
BCC	Behavioural change communication
CDC	U.S. Centers for Disease Control and Prevention
CHAI	Clinton Health Access Initiative
CQ	Chloroquine
CPD	Chloroproguanil-dapsone
CRT	Cluster-randomised trial
DHAPQ	Dihydroartemisinin-piperaquine (also referred to as *DHA-piperaquine)*
DLDB	*Duka la dawa baridi*
DMO	District Medical Officer
GPARC	Global Plan for Artemisinin Resistance Containment
GPS	Global positioning system
IHI	Ifakara Health Institute
KII	Key informant interview
MEMS™	Medication Events Monitoring Systems
MQ	Mefloquine
MSH	Management Sciences for Health
mRDT	Malaria rapid diagnostic test (also referred to as *rapid diagnostic test, RDT*)

NMCP	National Malaria Control Programme
Pf	*Plasmodium falciparum*
PQ	Primaquine
PMI	President's Malaria Initiative
Pv	*Plasmodium vivax*
QN	Quinine
RCT	Randomised Controlled Trial
RDT	Rapid diagnostic test (also referred to as *malaria rapid diagnostic test, mRDT*)
SEAM	Strategies for Enhancing Access to Medicines
SMS	Short message service (text messages)
SP	Sulfadoxine-pyrimethamine
TFDA	Tanzania Food and Drug Administration
THMIS	Tanzania HIV/AIDS and Malaria Indicator Survey
WHO	World Health Organization

1 Introduction

1.1 Overview of malaria

Malaria is a parasitic, febrile disease that continues to pose a major global health challenge, despite declining morbidity and mortality in recent years. Malaria is preventable and treatable, but in 2011-2012 caused an estimated 207 million cases and 627,000 deaths, with the vast majority of deaths occurring among children under five years in sub-Saharan Africa [1]. Of the estimated 3.4 billion people at risk of malaria, 1.2 billion are at high risk, mostly in sub-Saharan Africa. The poorest are disproportionately affected by malaria and most vulnerable to devastating socioeconomic consequences from their illness [2].

Malaria in humans is caused by five species of the parasite *Plasmodium* (*P. falciparum, P. vivax, P. ovale, P. malariae,* and the zoonotic species *P.knowlesi*). The most virulent is *P. falciparum,* which is responsible for the vast majority of severe malaria cases and malaria deaths. The parasites are transmitted by female Anopheles mosquitoes prevalent in Africa, Asia, and Latin America. Effective preventative measures include the use of insecticide-treated bed nets, indoor residual spraying, and prophylactic treatment of vulnerable populations [3].

Symptoms of uncomplicated malaria, such as fever and vomiting, are non-specific, resembling symptoms of many other bacterial and viral infections. As a result, patients who are treated presumptively for malaria may not be parasitaemic. To target treatment to patients who actually have malaria, the World Health Organization (WHO) now recommends the use of a diagnostic test for all suspected cases of malaria prior to treatment [4]. Access to prompt diagnosis and treatment is important, as uncomplicated malaria can rapidly progress to severe malaria, which is nearly always fatal if left untreated and has a case-fatality rate of up to 20% when treated [4]. Central to obtaining appropriate treatment is the choice and use of an effective antimalarial drug.

1.2 Antimalarial drugs and the challenge of resistance

Treatment for malaria has been characterised by the identification and widespread use of an antimalarial drug, followed by reducing efficacy as the malaria parasite responds to drug pressure and develops resistant genotypes that can survive treatment [5]. For many decades, chloroquine was the designated antimalarial drug of choice. Although resistance was first identified in the 1950s [6], the drug continued to be widely used, with sulfadoxine-pyrimethamine (SP) recommended where chloroquine failed. Like chloroquine, SP was also inexpensive ($0.10-0.20), well-tolerated and readily available, but resistance rapidly developed and spread across continents [7]. More expensive antimalarials such as mefloquine, halofantrine, and quinine were also used in Southeast Asia, though these drugs too became less effective over time [8].

The levels and spread of resistance from the 1980s to the 1990s corresponded to an increase in malaria-related deaths among children under five at a time when overall childhood mortality was decreasing [9]. This resulted in increased demand for and consensus around the adoption of combination therapies for malaria at the beginning of the 21st century. The rationale is that parasites exposed to two drugs would be less likely to become resistant to both of them and hence resistance would develop at a slower rate than when monotherapies are used [8]. Artemisinin-based combination therapies (ACTs) are preferred, as artemisinins have very high parasite killing rates, few known adverse effects, and are rapidly eliminated, ensuring that residual drug concentrations exert a low selection pressure on parasites [5]. Artemisinins also prevent production of gametocytes, reducing transmission potential [10, 11].

Among the first ACTs implemented were artesunate + mefloquine in 1994 on the Thai-Myanmar border [12] and artesunate + pyrimethamine-sulfadoxine in The Gambia in 1998 [13]. In early trials, ACTs were shown to be highly efficacious [13-15] and to reduce the spread of resistance in low transmission settings [12, 16]. Barnes *et al.* report on the impact of the first large-scale deployment of

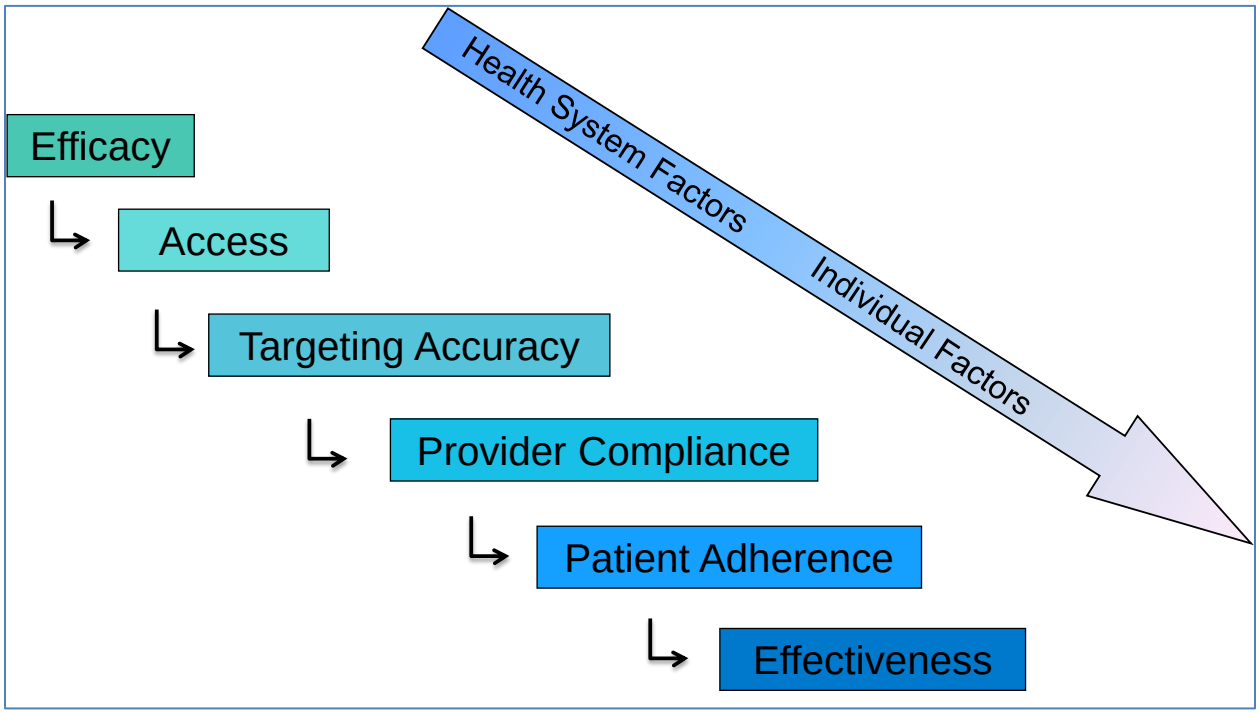
ACTs on the malaria disease burden in three countries in Africa [17]. In KwaZulu-Natal province of South Africa, treatment with co-formulated artemether-lumefantrine (AL) against a malaria epidemic began in January 2001, and vector control was scaled up. By the end of the year, malaria outpatient cases were reduced by 85%, and by 2003, outpatient cases and malaria admissions had each fallen by 99%, and malaria-related deaths by 97%. The improvements were sustained over seven years. Zambia was the first African country to adopt AL as first-line drug for uncomplicated malaria in 2002. By 2008 compared to 2001-2002, inpatient malaria cases and deaths were reduced by 61% and 66%, respectively, though this was partly attributed to improved vector control at the same time of AL implementation. Lastly, in Tigray, Ethiopia, AL was deployed through community health workers in 2005, and over a two-year period, the risk of malaria related mortality was lowered by 37%. In both Zambia and Tigray, AL was thought to be a major contributor to decreased prevalence of parasitaemia during the study periods.

ACTs are now recommended by WHO as first-line treatment of uncomplicated *P. falciparum* malaria [4] and have been rolled out in most malaria endemic countries [1]. While several different partner drug combinations exist, AL is the most common in Africa, followed by artesunate-amodiaquine [18]. ACTs continue to be effective in most parts of the world, including Africa. However, artemisinin resistance, characterised by slow parasite clearance [19], has emerged or spread in many parts of Southeast Asia and is now a major concern in western Cambodia and the Thailand-Myanmar border [20]. As there are no alternative drugs that will be available and affordable in endemic countries in the next several years, the spread of artemisinin resistance would be a public health crisis, especially if it became widespread in sub-Saharan Africa where the malaria burden is most severe. To contain the spread of resistance and to ensure that ACTs remain effective in other malaria-endemic regions, the Global Plan for Artemisinin Resistance Containment (GPARC) calls for malaria control and elimination measures in areas with observed resistance, such the Greater Mekong subregion [21].

1.3 The role of patient adherence in ensuring effectiveness

Achieving ACT effectiveness is a multi-step process dependent on a number of health systems and individual factors (Figure 1). The ACTs must be efficacious; patients must have access to an ACT provider with good quality ACTs in stock; the correct diagnosis must be made; providers must recommend ACT to patients with malaria; patients must obtain or purchase the ACT; and patients must be adherent to treatment [22-24]. The factors affecting each of these steps and their interactions are important for understanding the impact of interventions on ACT effectiveness and the overall public health impact of ACT treatment policies.

Figure 1: Pathway to Effectiveness (Source: The malERA Consultative Group on Health Systems and Operational Research [24], as appearing in Banek *et al.* 2014 [25])



This thesis focuses on patient adherence, the final step in the pathway from treatment efficacy to effectiveness. Patient adherence refers to correctly taking the full course of treatment (although as described in Chapter 2 of this thesis, there is considerable variation in the details of adherence definitions). Antimalarial regimens for uncomplicated malaria generally involve oral therapies and vary from one to 14 days, though most ACTs involve a 3-day regimen. The use of antimalarial drugs was previously reviewed by Yeung and White in 2004 [8], who found numerous examples of highly suboptimal adherence, including in some cases to ACTs. For example, in a study in Zambia, only 39% of patients took all doses of AL at the correct times [26]. Suboptimal adherence to ACTs is a concern for two key reasons, first for the effect on the likelihood of recovery for patients taking ACTs, and secondly for the potential implications on hastening the development of drug resistance.

Implications for treatment failure. While clearly patients must take the medication to realise therapeutic benefits, there is surprising little data on how adherent to ACTs patients must be in order to prevent treatment failure. Early trials showed that six-dose regimens of AL had higher cure rates (> 96%) compared to a four-dose regimen (83%), suggesting that six doses are needed to optimise effectiveness [27, 28]. Cure rates for ACTs have been very high for both supervised and unsupervised treatment groups. One study reported slightly higher treatment failure rates to artesunate-mefloquine in an unsupervised group compared to a supervised group (3.9% vs. 0.0%, p=0.015) [29], while another study comparing treatment with AL and quinine in Uganda reported in a multivariate analysis of AL and quinine groups combined that taking more than 80% of pills was associated with reduced treatment failure [30]. There have also been accounts of patients who did not receive correct doses for their weight or received poor quality drugs and experienced treatment failure [31, 32].

Implications for drug resistance. In addition to causing treatment failure, sub-therapeutic drug concentrations resulting in recrudescence can select for resistant parasites [33, 34]. This occurs when drug concentrations are sufficient to suppress sensitive parasites, but newly arisen mutant parasites

survive and produce sufficient gametocytes for transmission [34]. There is some evidence that current dosing recommendations are inadequate for hyperparasitaemic patients and vulnerable groups such as young children and pregnant women, and these under-dosed patients may contribute most to drug pressure [31]. Patient adherence is thus one important factor in ensuring sufficient drug concentrations to avoid resistance.

1.4 The role of the private for-profit sector

Antimalarial drugs are available at public health facilities, private not-for-profit health facilities, private for-profit outlets, and community health workers. In some countries (e.g. Zambia), public health facilities are the most common source of antimalarials, but in some countries (e.g. Nigeria and Democratic Republic of Congo) treatment is more frequently sought at private for-profit outlets [35], and in many settings such outlets are an important source of care [36-39]. Data synthesised across household surveys in sub-Saharan Africa indicate that in 2013, of children under five years with fever who reported receiving drugs, 35% visited the private for-profit sector [40]. Where data are available for all age groups it appears that the private sector is an even more important source of medicines in older children and adults [40-42].

Types of private for-profit outlets include private facilities, pharmacies, drug stores, general retailers, and itinerant vendors [43], with the dominant type varying between countries. For example, in Ghana, Nigeria, Tanzania and Uganda drug stores are the most common type of private for-profit outlet stocking antimalarials, while in Madagascar and Niger general retailers are most common [43, 44].

Preference for private for-profit outlets may be motivated by factors such as their longer opening hours, proximity, speed of service, approachability of providers, availability of drugs, lower costs or availability of credit, and dissatisfaction with health facilities [39, 45-47]. However, substandard

practices have also been noted in drug stores, including dispensing of inappropriate or ineffective drugs, dispensing of incorrect doses, and inadequate knowledge of medication instructions [39, 48].

Since their introduction, the expense of ACTs has limited their availability in the private sector [49, 50]. The proportion of private sector clients obtaining ACTs has increased over time as ACTs have become more widely known, and their price has fallen, particularly in some settings where they have been subsidised by programs such as the Affordable Medicines Facility- malaria (AMFm) [51]. For example, in 2011 the percentage of private for-profit outlets stocking antimalarials that stocked quality-assured ACTs was over 60% in five of the AMFm settings (Ghana, Kenya, Tanzania-mainland, Uganda and Zanzibar), though less than 15% in two other AMFm countries (Madagascar and Niger), and just above 20% in two non-AMFm countries (Benin and Zambia) [44, 52, 53].

As ACTs become more available in the private sector, monitoring how they are used becomes important to maximise their benefits. One might expect lower adherence from some private for-profit providers such as drug shops if dispensers are less likely than their public sector counterparts to provide appropriate doses or advice. While a number of interventions have been targeted at improving the practices of such drug retailers [54-57] few have focused on strategies to increase patient adherence to the antimalarials they provide [58-62]. There is thus a need for further study of the nature of antimalarial adherence among patients treated by private retailers, and of interventions to enhance this.

1.5 Thesis aims and overview

This thesis adds to the limited literature on patient adherence to ACTs obtained in the private for-profit sector by comparing adherence to ACTs obtained in public health facilities and private drug stores and describing an evaluation of an intervention to improve retail staff knowledge and patient adherence. In addition, the thesis addresses the methodological challenges of measuring patient adherence to ACTs.

Chapter 2 highlights key gaps in understanding and measurement of adherence in an updated literature review on adherence to antimalarial drugs, including recent studies on adherence to ACTs. An overview of the setting and context of the research is presented in Chapter 3, and objectives and methods are outlined in Chapter 4. Chapter 5 presents a text message intervention targeted at dispensers in private drug shops to improve their knowledge of advice to provide when dispensing AL and to assess the effects on patient adherence. Chapter 6 compares patient adherence to AL obtained in the private and public sectors and factors associated with adherence in each setting. Methods of assessing patient adherence are explored in Chapter 7, which also reports on the use of smart blister packs that recorded the date and time each pill was removed from packaging. Finally, Chapter 8 reviews the main findings of the thesis and discusses methodological strengths and limitations, as well as implications for future research and policy.

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2 Literature review

2.1 Introduction

This chapter contains a systematic literature review entitled “How patients take malaria treatment: A systematic review of the literature on adherence to antimalarial drugs” that was published in PLOS ONE in January 2014. Following the literature review in Section 2.2, updates to the review and concluding thoughts are described in Section 2.3.

2.2 Literature review (cover sheet on next page)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Katia Bruxvoort
Principal Supervisor	David Schellenberg
Thesis Title	Evaluating patient adherence to aretemether-lumefantrine obtained from public and private drug outlets in Tanzania

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	PLOS ONE		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had the primary role of designing and conducting the review, abstracting the data, analysing results, and drafting the paper.

Student Signature: Katia Bruxvoort **Date:** 14 Dec 2014

Supervisor Signature: DS **Date:** 15 Dec 14

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How Patients Take Malaria Treatment: A Systematic Review of the Literature on Adherence to Antimalarial Drugs

Katia Bruxvoort[1,2]*, Catherine Goodman[1], S. Patrick Kachur[3], David Schellenberg[1]

1 London School of Hygiene and Tropical Medicine, London, United Kingdom, **2** Ifakara Health Institute, Dar es Salaam, Tanzania, **3** United States Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

Abstract

Background: High levels of patient adherence to antimalarial treatment are important in ensuring drug effectiveness. To achieve this goal, it is important to understand levels of patient adherence, and the range of study designs and methodological challenges involved in measuring adherence and interpreting results. Since antimalarial adherence was reviewed in 2004, there has been a major expansion in the use of artemisinin-based combination therapies (ACTs) in the public sector, as well as initiatives to make them more widely accessible through community health workers and private retailers. These changes and the large number of recent adherence studies raise the need for an updated review on this topic.

Objective: We conducted a systematic review of studies reporting quantitative results on patient adherence to antimalarials obtained for treatment.

Results: The 55 studies identified reported extensive variation in patient adherence to antimalarials, with many studies reporting very high adherence (90–100%) and others finding adherence of less than 50%. We identified five overarching approaches to assessing adherence based on the definition of adherence and the methods used to measure it. Overall, there was no clear pattern in adherence results by approach. However, adherence tended to be higher among studies where informed consent was collected at the time of obtaining the drug, where patient consultations were directly observed by research staff, and where a diagnostic test was obtained.

Conclusion: Variations in reported adherence may reflect factors related to patient characteristics and the nature of their consultation with the provider, as well as methodological variations such as interaction between the research team and patients before and during the treatment. Future studies can benefit from an awareness of the impact of study procedures on adherence outcomes, and the identification of improved measurement methods less dependent on self-report.

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* E-mail: katia.bruxvoort@lshtm.ac.uk

Introduction

While considerable progress has been made in the last decade to reduce malaria morbidity and mortality, malaria continues to cause more than 200 million cases and more than 600,000 deaths per year [1]. The vast majority of deaths occur among children under five in Africa, though many other parts of the world are also affected. Malaria is entirely preventable and treatable, but if treatment is delayed or ineffective, the parasite burden may rapidly increase and cause severe malaria, which has a case fatality rate of 10–20% even among those receiving treatment [2]. Resistance of parasites to antimalarials, exacerbated by their widespread and indiscriminate use, threatens the effectiveness of malaria treatment.

In order for antimalarial treatment to be effective, multiple steps must occur [3–4]. The patient must promptly seek care, the correct diagnosis must be made; the correct drug and dose must be recommended; the drug must be efficacious, of good quality and in stock; the patient must receive or purchase the correct dose; and the correct dose must be taken with correct timing until all doses are complete. Not only can incomplete dosage result in treatment failure, but it may arguably contribute to the spread of resistance [5–6]. Sub-therapeutic treatment can result in recrudescence and select for resistant parasites [7]. Patient adherence, defined as correctly taking the full therapeutic course of treatment, is thus a critical step in ensuring antimalarial effectiveness and reducing malaria mortality.

To achieve this goal, it is important for policymakers to understand levels of patient adherence to antimalarials, how they

vary by context, and how adherence can be improved. However, studies measuring patient adherence encounter substantial methodological challenges, such as selection of appropriate definitions of adherence and appropriate measurement methods. This results in a broad diversity of study designs which, along with the wide range of study contexts and different antimalarial drugs, can challenge interpretation of adherence results.

The use of antimalarial drugs was last reviewed by Yeung and White in 2004 [8]. Of the 22 studies they identified in Africa, Asia and South America that reported quantitative data on patient adherence, only five assessed adherence to artemisinin-based combination therapies (ACTs), and only eight studies, mostly household surveys, measured adherence to antimalarials obtained through community health workers or drug retailers. Since publication of this review, there has been a major expansion of the availability of ACTs, which have been shown to be efficacious and may reduce the spread of resistance in low transmission settings [9–12]. Due to the development of resistance to older antimalarials, such as chloroquine and sulfadoxine pyrimethamine (SP), ACTs have become the first-line treatment for *Plasmodium falciparum* malaria in the public sector in most malaria-endemic countries. In addition, a growing number of initiatives to increase ACT use through community health workers and private sector providers have been implemented [13]. Furthermore, a large number of new studies assessing adherence to antimalarials, particularly to ACTs, have been conducted in the last nine years, raising the need for an update on this topic.

Here, previously reviewed and recent studies providing quantitative results on adherence to antimalarials obtained for treatment are analysed. We examine how results vary by definition of adherence and key methodological characteristics, and we present the studies' own findings on factors associated with adherence. We emphasize challenges in measuring adherence, avoiding bias, and implications for future research.

Methods

Studies included in this review were identified by three methods. First, a systematic literature search was conducted on PubMed using MeSH and free text terms as follows: (Medication Adherence (MeSH) or Patient Compliance (MeSH) or compliance or adhere*) and (Antimalarials (MeSH) or antimalarial*). Secondly, reference lists from studies and reviews identified were searched manually for relevant studies. Finally, researchers known to be currently active in the field were contacted.

Studies that were clearly irrelevant were immediately discarded, and abstracts and manuscripts of the remaining studies were examined in detail to determine relevance. Published studies that provided quantitative data on patient adherence to antimalarials obtained for treatment of malaria were included in this review. Where papers employed both quantitative and qualitative methods, only the quantitative results are reported here. Studies were included from all parts of the world in any language utilizing various study designs, including household surveys and clinical trials examining the effectiveness of supervised versus unsupervised treatment that specifically reported data on adherence in the unsupervised arm. Studies assessing adherence to antimalarials obtained for prophylaxis, and effectiveness studies that did not report data on adherence were excluded. Manuscripts of studies meeting inclusion criteria were read in detail and data on study settings, objectives, study design, definitions of adherence, methods of assessing adherence and results were systematically reviewed and abstracted into a database.

Results

The initial literature search using PubMed identified 1340 studies (Figure 1). In total, 49 studies were retained from the initial search. Many of the excluded studies referred to antimalarials obtained for prophylaxis or treatment of conditions other than malaria. Manual examination of reference lists and personal communication with other researchers in the field identified six additional studies, making a total of 55 studies.

Characteristics of studies included

Three main types of studies were identified: descriptive studies, interventions to improve adherence, and studies with clinical outcomes as a primary endpoint (Tables 1–3). While there is clearly some overlap between types, studies were categorised as descriptive except for those that described an intervention to improve adherence or simultaneously measured clinical outcomes and patient adherence. Distinguishing studies with clinical outcomes is helpful, as they were often conducted under relatively controlled conditions, or with relatively intensive follow-up, which may have influenced adherence results.

More than half of the 55 studies were descriptive (30 studies) [4,14–42]. The majority of these (21 studies) were observational follow-up studies [14–34], where patients obtaining a drug were visited at their home or returned to the drug outlet after a specified number of days, at which time adherence data were collected. While most follow-up studies were prospective, two studies retrospectively identified patients to follow-up for adherence assessments [21,25]. Several of these studies were part of larger studies that included an intervention (e.g. use of community health workers [15,24] or subsidization of ACTs in private retail outlets [16]), but did not provide information on the impact on adherence through pre and post or control group comparisons, so the studies were categorised as "descriptive" in terms of their assessment of adherence. Eight studies used household surveys to collect descriptive data [35–42], and one study used both household survey and follow-up methods [4]. In these household surveys, households in selected areas were visited without prior knowledge of who had obtained antimalarial drugs, and interviews were conducted about episodes of illness occurring in the weeks prior to the survey, treatment obtained, and adherence.

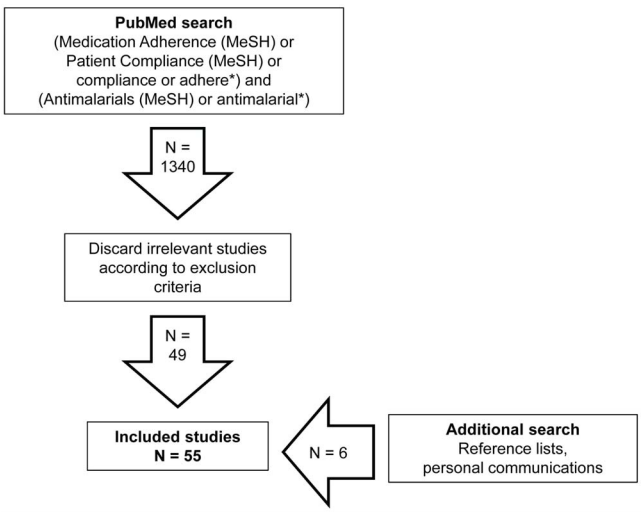

Figure 1. Literature search results.
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Table 1. Characteristics of studies included in the review (by author) for descriptive studies.

Study, (Country), Source(s) of drugs	Drug regimen(s)[1]	Method(s) of assessing adherence	Approach(es) to assessing adherence[2]	Day of follow-up visit (Day 1 = drug dispensed)	Level of adherence (N = denominator)
Abuaku et al. 2004 [35], (Ghana), Multiple sources	SP, chloroquine (CQ), & amodiaquine (AQ)	Household survey questionnaire	Completed treatment	n/a	SP - 100% (N = 4); CQ - 11.1% site 1 (N = 171); CQ - 36.4% site 2 (N = 195); AQ - 12.9% site 1 (N = 9); AQ - 50% site 2 (N = 2)
Ajayi et al. 2008 [36], (Ghana, Nigeria, Uganda), Community health workers	AL in Nigeria and Uganda & artesunate-amodiaquine in Ghana	Household survey questionnaire	Completed treatment	n/a	Ghana - 97% (N = 153); Nigeria - 93% (N = 60); Uganda - 81% (N = 31); Overall - 94% (N = 244)
Amin et al. 2004 [37], (Kenya)	SP & amodiaquine	Household survey questionnaire	*Unique approach* = patients who took a higher dose than recommended or an adequate dose	n/a	SP - 66.7% (N = 78); AQ - 13.8% (N = 94)
Barnes et al. 2005 [38], (South Africa), Health facilities	AL	Household survey questionnaire	Completed treatment	n/a	96% (N = 235)
Beer et al. 2009 [14], (Zanzibar), Health facilities	Artesunate-amodiaquine (3 days)	Self-report, pill count	Verified completed treatment & *Unique approach* = Verified completed treatment, plus child did not vomit dose, or another dose was administered if child vomited first dose	Day 4	Verified completed treatment - 77% (N = 174); *Unique approach* - 63% (N = 174)
Chinbuah et al. 2006 [15], (Ghana), Community health workers	AL (3 days)	Self report	Timely completion	Day 4	100% (N = 334)
Cohen et al. 2012 [16], (Uganda), Private drug shop	AL (3 days)	Self-report, pill count	Verified completed treatment	Day 4	65.8% (N = 152)
Deming et al. 1989 [39], (Togo), Multiple sources	Chloroquine	Household survey questionnaire	Completed treatment	n/a	29% (N = 370)
Depoortere et al. 2004 [17], (Zambia), Health facility (refugee)	SP + artesunate (3 days)	Self-report, pill count	Verified timely completion	Day 4	39.4% (N = 162)
Depoortere et al. 2004 [18], (So. Sudan), Health facility	AL (3 days)	Self-report, pill count	Verified timely completion	Day 4	59.1% (N = 93)
Fogg et al. 2004 [19], (Uganda), Health facilities	AL (3 days)	Self-report, pill count, lumefantrine assay[3]	Verified timely completion	Day 4	90% (N = 210)
Gerstl et al. 2010 [20], (Sierra Leone), Health facilities	Artesunate-amodiaquine (3 days)	Self-report, pill count	Verified timely completion	Day 4	48% (N = 118)
Kabanywanyi et al. 2010 [22], (Tanzania), Health facility	AL (3 days)	Self-report	Timely completion & Completed treatment	Randomized to follow-up visit close to time of one of the five doses to be taken at home	Timely completion - 90% (N = 552); Completed treatment - 98% (N = 552)
Kachur et al. 2004 [23], (Tanzania), Health facility	SP + artesunate (3 days)	Self-report, pill count	Timely completion & Verified timely completion	After 48 hours	Timely completion - 76.6% (N = 128); Verified timely completion - 75% (N = 128)
Kalyango et al. 2013 [24], (Uganda), Community health workers	AL (3 days)	Self-report, pill count	Verified completed treatment & *Unique approach* = took as prescribed with fatty meals at each dose and no vomiting within 30 minutes	Day 4	Verified completed treatment - 86% (N = 667); *Unique approach* - 16.9% (N = 667)

Table 1. Cont.

Study, (Country), Source(s) of drugs	Drug regimen(s)[1]	Method(s) of assessing adherence	Approach(es) to assessing adherence[2]	Day of follow-up visit (Day 1 = drug dispensed)	Level of adherence (N = denominator)
Khantikul et al. 2009 [25], (Thailand), Health facilities	Chloroquine + primaquine (14 days)	Self-report	Completed treatment	Up to one year	24.8% (N = 206)
Kolaczinski et al. 2006 [26], (Uganda), Health facilities	Chloroquine + SP (3 days)	Self-report, pill count	Verified completed treatment	Day 4	96.3% (N = 241)
Krause & Sauerborn 2000 [4], (Burkina Faso), Multiple sources	Antimalarial drugs (mostly chloroquine & quinine)	Pill count	*Unique approach* = drugs taken correctly according to count of pills in the middle of the treatment course	Middle of the treatment course	68% (N = 47)
Lawford et al. 2011 [27], (Kenya), Health facilities	AL (3 days)	Self-report, pill count	Verified completed treatment	Day 4	64.1% (N = 918)
Lemma et al. 2011 [28], (Ethiopia), Community health workers	AL (3 days)	Self-report, pill count	Verified timely completion & Completed treatment	Day 4	Verified timely completion - 38.7% (N = 155); Completed treatment - 73.5% (N = 155)
Mace et al. 2011 [29], (Malawi), Health facilities	AL (3 days)	Self-report, pill count	Verified timely completion & Verified completed treatment	Day 4	Verified timely completion - 65% (N = 386); Verified completed treatment - 75% (N = 386)
Nshakira et al. 2002 [30], (Uganda), Multiple sources	Chloroquine (3 days)	Self-report	Completed treatment	Day 4	37.8% (N = 463)
Nsungwa-Sabiiti et al. 2005 [40], (Uganda), Multiple sources	Chloroquine & chloroquine + SP	Household survey questionnaire	Completed treatment	n/a	25% (N = 65)
Onyango et al. 2012 [41], (Kenya), Multiple sources	AL	Household survey questionnaire	Completed treatment	n/a	47% (N = 297)
Peeters Grietens et al. 2010 [21], (Peru), Health facilities	Primaquine (7 days)	Self-report, triangulation with health centre records	Completed treatment & *Unique approach* = self-reported adherence plus health centre records verifying that patients returned to receive the last four doses of primaquine	Up to one year	Completed treatment - 71.9% (N = 185); *Unique approach* - 62.2% (N = 185)
Pereira et al. 2011 [31], (Brazil), Health facilities	Chloroquine + primaquine (7 days)	Self-report, pill count	Verified timely completion	Day 7	86.4% (N = 280)
Reilley et al. 2002 [32], (Sri Lanka), Health facility	Chloroquine + primaquine (5 days)	Self-report	Completed treatment	Day 6	74% (N = 132)
Simba et al. 2012 [33], (Tanzania), Health facilities	AL (3 days)	Self-report, lumefantrine assay[3]	Timely completion	Day 7	88.3% (N = 444)
Thera et al. 2000 [42], (Mali), Multiple sources	Chloroquine	Household survey questionnaire	Completed treatment	n/a	37.8% (N = 152)
Twagirumukiza et al. 2010 [34], (Rwanda), Health facility	Quinine tablets (7 days, last 4 unsupervised)	Self-report, pill count, electronic pill boxes	Verified timely completion & *Unique approach* = percentage of doses taken according to electronic pill box	Day 8	Verified timely completion - 100% (N = 56); *Unique approach* - 82.7% (N = 56)

[1]Duration of drug regimen in days not given for household surveys;
[2]See Table 4 for definitions of approaches;
[3]Not incorporated into approach to assessing adherence.
doi:10.1371/journal.pone.0084555.t001

Table 2. Characteristics of studies included in the review (by author) for studies assessing interventions to improve adherence.

Study, (Country), Source(s) of drugs	Drug regimen(s)[1]	Intervention	Method(s) of assessing adherence	Approach(es) to assessing adherence[2]	Day of follow-up visit (Day 1 = drug dispensed)	Level of adherence without intervention (N = denominator)	Level of adherence with intervention (N = denominator)
Agyepong et al. 2002 [43], (Ghana), Health facility	Chloroquine (3 days)	Drug labels & verbal instructions	Self-report	Timely completion & *Unique approach* = at least the minimum dose or higher taken once per day	Day 4	Timely completion[4] - 24% (N = 205); *Unique approach* - 45% (N = 205)	Timely completion (control) - 27% (N = 78); Timely completion (intervention) - 39% (N = 121); *Unique approach* (control) - 44% (N = 78); *Unique approach* (intervention) - 78% (N = 121)
Ansah et al. 2001 [44], (Ghana), Health facility	Chloroquine (3 days)	Introduction of tablets to replace syrup	Self-report, pill count or measurement of remaining syrup[3]	Timely completion	Day 4	42% (N = 144)	91% (n = 155)
Denis et al. 1998 [45], (Cambodia), Multiple sources	Quinine + tetracycline (7 days)	Posters & video	Self-report, pill count[3]	Completed treatment	Day 7 (Day 4 if doses were purchased for only 3 days)	Group 1 - 1% (N = 95); Group 2 - 10% (N = 82)	Group 1 (posters and video) - 39% (N = 88); Group 2 (posters only) - 15% (N = 120)
Kangwana et al. 2011 [46], (Kenya), Multiple sources	AL (3 days)	Subsidised AL, shopkeeper training, & community awareness activities	Self-report	Completed treatment	n/a	Group 1 - 40.5% (N = 26); Group 2 - 53.1% (N = 30)	Group 1 (control) - 24.8% (N = 89); Group 2 (intervention) - 67% (N = 221)
Lauwo et al. 2006 [47], (Papua New Guinea), Health facility	Chloroquine + SP (3 days)	Packaging & counselling	Self-report	Timely completion	Day 4	76.5% (N = 119)	Counselling - 92.9% (N = 112); Counselling & packaging - 95.5% (N = 91)
Marsh et al. 1999 [48], (Kenya), Private drug shops	Chloroquine	Shopkeeper training	Household survey questionnaire; laboratory assay in a subset of children given a full dose[3]	Completed treatment	Day 4	3.7% (N = 109)	75% (N = 108)
Marsh et al. 2004 [49], (Kenya), Private drug shops	Chloroquine & SP	Shopkeeper training	Household survey questionnaire	Completed treatment	n/a	Chloroquine - 8% (N = 160)	SP - 64% (N = 441)
Okonkwo et al. 2001 [50], (Nigeria), Health facilities	Chloroquine	Pictorial insert & verbal instructions	Self-report, measurement of remaining syrup	Verified timely completion	48 hours after start of treatment	36.5% (N = 190)	Pictorial insert - 51.9% (N = 225); Pictorial insert & verbal instructions - 73.3% (N = 217)
Qingjun et al. 1998 [51], (China), Health facilities	Chloroquine + primaquine (8 days)	Packaging	Self-report, laboratory assay	Timely completion & Biological assay (by phenobarbital markers)	Day 4 or Day 9	Timely completion - 83% (N = 163); Biological assay - 80.5% (N = 134)	Timely completion - 97% (N = 161); Biological assay - 97% (N = 138)
Shwe et al. 1998 [52], (Myanmar), Health facilities	Artesunate + mefloquine (3 days)	Packaging & training	Laboratory assay	Biological assay (by chloroquine & quinine markers)	Day 7	n/a	99.5% (N = 380)
Sirima et al. 2003 [53], (Burkina Faso), Community health workers	Chloroquine	Packaging & availability through community health workers	Household survey questionnaire	Completed treatment	n/a	n/a	52% (N = 1806)
Winch et al. 2003 [54], (Mali), Community health workers	Chloroquine (3 days)	Community health worker training	Self-report, pill count or measurement of remaining syrup	Timely completion & *Unique approach* = Timely completion or higher dose than recommended	Day 4	Timely completion - 1.5% (N = 131); *Unique approach* - 21.6% (N = 131)	Timely completion - 42.1% (N = 151); *Unique approach* - 71.7% (N = 151)

Table 2. Cont.

Study, (Country), Source(s) of drugs	Drug regimen(s)[1]	Intervention	Method(s) of assessing adherence	Approach(es) to assessing adherence[2]	Day of follow-up visit (Day 1 = drug dispensed)	Level of adherence without intervention (N = denominator)	Level of adherence with intervention (N = denominator)
Yeboah-Antwi et al. 2001 [55], (Ghana), Health facilities	Chloroquine (3 days)	Age-based packaging of syrup & tablets	Self-report, pill count or measurement of remaining syrup[3]	Timely completion	Day 4	Tablets - 60.5% (N = 152); Syrup - 32.6% (N = 95); Overall - 49.8% (N = 247)	Tablets - 82.0% (N = 167); Syrup - 54.7% (N = 95); Overall - 72.1% (N = 262)

[1]Duration of drug regimen in days not given for household surveys;
[2]See Table 4 for definitions;
[3]Not incorporated into adherence definition;
[4]Weighted results for three control and three intervention clinics.
doi:10.1371/journal.pone.0084555.t002

Thirteen studies evaluated interventions to improve adherence [43–55]. Of these, seven were randomized controlled trials (RCTs) [44,46–47,50–51,54–55], two were controlled pre- and post-intervention studies [43,45], two were uncontrolled pre- and post-intervention studies [48–49], and two were post-intervention only adherence assessments [52–53]. Follow-up methods were used by eight of the thirteen intervention studies, while the remaining four used household surveys. The interventions included new packaging with and without training, including pre-packaging of two component drugs together and pictorial inserts to packaging [47,50–53,55], as well as dispenser training of shopkeepers [48–49] or community health workers [54]. Ansah *et al.* (2001) [44] conducted an RCT of chloroquine tablets for children compared to chloroquine syrup, while Denis *et al.* (1998) [45] evaluated videos and posters as community health education strategies to improve adherence to a 7-day regimen of quinine + tetracycline.

The third type of studies, those assessing clinical outcomes as a primary endpoint in addition to reporting patient adherence, included seven RCTs comparing effectiveness and adherence of different drug regimens [56–60] or supervised versus non-supervised treatment [61–62], and four uncontrolled studies also assessing effectiveness and adherence [63–66], all of which employed follow-up methods. In addition, a prospective open cohort study examined the association of previous compliance with antimalarials for malaria caused by *P. falciparum* or *P. vivax* and occurrence of malaria during follow-up [67].

Of the 55 studies, 40 took place in Africa, 11 in Asia, and four in Latin America. Subjects included all age groups in 25 studies, only children under five in 19 studies, both children under five and older children in an additional seven studies, and only adults in four studies. Most studies assessed adherence to antimalarials taken to treat infection with *P. falciparum*, with five studies focusing on treatment for *P. vivax* [21,25,31,51,62], and three studies on treatment for both species [32,66–67]. Most studies assessed adherence to treatment obtained in health facilities or malaria clinics. Four follow-up studies evaluated adherence to drugs obtained from community agents [15,24,28,54] three took place in the context of complex humanitarian emergencies [17–18,26], and three were conducted from private drug shops [16,30,45]. Most household surveys reported adherence to antimalarials obtained from both public and private sectors, except for four that focused on interventions to improve adherence to antimalarials obtained from drug shops [48–49] or community health workers [36,53].

Patient adherence to more than one drug regimen was assessed in 12 studies, while 43 studies reported adherence to a single drug (Tables 1–3). Adherence to ACTs was assessed in 26 studies. Artemether-lumefantrine (AL) was the ACT in 18 of these studies, with two of these 18 also reporting adherence to artesunate-amodiaquine [36,60]. Other ACTs evaluated included two additional studies of artesunate-amodiaquine [14,20], as well as SP + artesunate [17,23] and artesunate + mefloquine [52,63–64]. Non-artemisinin-based combinations featured in 13 studies (chloroproguanil-dapsone (CPD) [57–58], quinine + doxycycline or tetracycline [45,59,67], chloroquine + SP [26,40,47], SP + amodiaquine [65] and, for treatment of *P. vivax* malaria, chloroquine + primaquine [25,31–32,51,62,66–67]). Adherence to chloroquine and other monotherapies was assessed in 20 studies.

Definitions of adherence and measurement methods

The 55 studies reviewed here employed a wide range of definitions and methodologies. Adherence was measured by questionnaires containing varying detail about how and when drugs were taken (self-report); physical counts of tablets remaining

Table 3. Characteristics of studies included in the review (by author) for studies with clinical outcomes which also report adherence.

Study, (Country), Source(s) of drugs	Drug regimen(s)[1]	Approach(es) to assessing adherence[2]	Approach(es) to assessing adherence[2]	Day of follow-up visit (Day 1 = drug dispensed)	Level of adherence with intervention (N = denominator)
Achan et al. 2009 [56], (Uganda), Health facility	AL (3 days) & quinine (7 days)	Self-report, pill count	*Unique approach* = percentage of pills taken	Day 4	AL - 94.5% (N = 85); Quinine - 85.4% (N = 75)
Bell et al. 2009 [57], (Malawi), Health facility	AL (3 days) & chloroproguanil-dapsone (CPD, 3 days)	Self-report, electronic pill boxes, laboratory assays[3]	Completed treatment & *Unique approach* = electronic pill bottle opened once on Day 1 & two times each on Days 2 & 3	Day 8	Completed treatment (AL) - 100% (N = 185); Completed treatment (CPD) - 99.2% (N = 371); *Unique approach* (AL) - 92% (N = 87); *Unique approach* (CPD) - 90.6% (N = 181)
Congpuong et al. 2010 [63], (Thailand), Health facilities	Artesunate + mefloquine + primaquine (3 days)	Self-report, drug assays	Completed treatment & Biological assay	Day 4	Completed treatment - 100% (N = 240); Biological assay (mefloquine marker) - 96.3% (N = 215); Biological assay (quinine marker) - 98.5% (N = 214)
Duarte et al. 2003 [67], (Brazil), Health facilities	Quinine + doxycycline (7 days) & primaquine + chloroquine (14 days)	Self-report	Completed treatment	Up to 4 months	83.8% (N = 488)
Dunyo et al. 2010 [58], (The Gambia), Health facilities	AL (3 days) & chloroproguanil-dapsone (CPD, 3 days)	Self-report (pill count for some[3])	Completed treatment	Day 4	AL - 67% (N = 600); CPD - 94% (N = 599)
Faucher et al. 2009 [60], (Benin), Health facility	AL (3 days) & artesunate-amodiaquine (ASAQ) (3 days)	Self-report, pill count	Verified completed treatment	Day 4	AL - 83% (N = 96); ASAQ - 91% (N = 96)
Fungladda et al. 1998 [59], (Thailand), Health facility	Artesunate (4 days) & quinine + tetracycline (7 days)	Self-report, pill count	Verified completed treatment	Day 5 or Day 8	Artesunate - 98.4% (N = 61); Quinine + tetracycline - 71.7% (N = 53)
Na-Bangchang et al. 1997 [64], (Thailand), Health facilities	Artemether + mefloquine (2 days)	Laboratory assays	Biological assay	Day 3	86.8% (N = 106)
Rahman et al. 2008 [61], (Bangladesh), Health facility	AL (3 days)	Self-report, pill count, lumefantrine assay[3]	Verified timely completion	Day 4	93% (N = 160)
Souares et al. 2008 [65], (Senegal), Health facilities	SP + amodiaquine (3 days)	Self-report, laboratory assays[3]	Timely completion & *Unique approach* = at least 80% of the prescribed dose of each of the two drugs was taken	Day 4	Timely completion - 37.7% (N = 289); *Unique approach* - 64.7% (N = 289)
Takeuchi et al. 2010 [62], (Thailand), Health facility	Chloroquine + primaquine (14 days)	Self-report	Completed treatment	Day 8 & Day 15	85% (N = 101)
Yepez et al. 2000 [66], (Ecuador), Health facilities	Chloroquine + primaquine (3 days for *Pf* & 7 days for *Pv*)	Self-report	Timely completion	Day 4 or Day 8	*Pf* - 79.2% (N = 120); *Pv* - 58.5% (N = 129); Overall - 68.3% (N = 249)

[1]Duration of drug regimen in days not given for household surveys;
[2]See Table 4 for definitions;
[3]Not incorporated into adherence definition
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Table 4. Approaches to assessing patient adherence across studies.

Approach	Definition	Method	Number of studies[1]
Completed treatment	Patient completed treatment	Self-report	28
Verified completed treatment	Patient completed treatment	Self-report and pill count	10
Timely completion	Patient exactly followed instructions in terms of dose, frequency and duration	Self-report	12
Verified timely completion	Patient exactly followed instructions in terms of dose, frequency and duration	Self-report and pill count	11
Biological assays	Sufficient levels of drug(s) in biological samples	Biological assays	4
Unique approaches	Various	Various	11

[1]All studies are included if adherence is reported by at least one of these five approaches (n = 52 studies) and are included more than once if multiple approaches were used.

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in packaging or dispensing envelopes (pill counts) and volumetric measurement of syrups; pill containers with electronic caps that record the date and time of each opening (electronic pill boxes); assays for drug levels in biological samples; and composites of these methods.

At least one approach used in 52 of the 55 studies could be classified under one of five overarching approaches defined for the purpose of this review, based on both the nature of adherence required and the method used to measure adherence (Table 4). "Completed treatment" identifies individuals who said they completed treatment. "Verified completed treatment" refers to reported completed treatment that is corroborated by a pill count. "Timely completion" refers to patients reporting that they completed each dose at an appropriate time. "Verified timely completion" identifies those reporting timely completion with a pill count to confirm that no tablets were left. Lastly, "biological assay" refers to detection of sufficient levels of drugs in biological samples.

Correct timing of doses, involving the correct dose, frequency, and duration, was required in 22 studies ("timely completion" and "verified timely completion"), 11 of which were studies of ACTs. However, there was considerable variation in which intervals were considered "correct", "recommended" or "prescribed". Several studies calculated the expected time of each dose per the manufacturer's instructions and allowed an interval of several hours on either side [22–23,28], while other studies required the correct dose to be taken on each day specified, or for AL twice per day for three days [15,18,33,61], and other studies did not report exactly what was considered correct. This is in contrast to assessments of "completed treatment" and "verified completed treatment", which did not require correct timing of doses. Furthermore, many studies reported in their methods that drug packaging was inspected, but only 21 studies specifically incorporated pill counts into adherence definitions, requiring self-reported adherence verified by empty packages or the expected number of remaining pills ("verified completed treatment" and "verified timely completion").

Adherence results

The studies reported a very wide range of results for the percentage of patients adherent, ranging from 1.5% to 100% across different studies and settings. Below we explore how the results varied firstly by the approach to assessing adherence and data collection, secondly by antimalarial and outlet type, and thirdly by the nature of the interaction between patients and dispensers or researchers during the study. Scatter plots are used to facilitate the identification of general patterns in these results. Finally we present the studies' own findings on factors found to be associated with adherence in multivariate models.

(i) Variation by approach and data collection method

Figure 2 shows a comparison of adherence results by the five approaches. The plot includes multiple points from studies which used more than one approach to report adherence. Studies that did not use any of the five approaches were not plotted [4,37,56]. In addition, when results of adherence to the same drug were reported from more than one study site within the same country, the weighted average of these sites was plotted [35,45]. For intervention studies, only baseline results were plotted in order to represent standard practice; thus, two studies were not plotted since they provided adherence results post-intervention only [52–53]. When multiple non-overlapping degrees of adherence were used (such as *definitely non-adherent*, *probably non-adherent*, *probably adherent*), the most adherent level was considered the proportion adherent for the purpose of Figure 2.

Overall, it does not appear that using stricter approaches involving correct dose timing ("timely completion" and "verified timely completion") or requiring pill counts in addition to self-reported histories ("verified completed treatment" and "verified timely completion") are associated with lower adherence, but this does not account for differences in contexts and methodologies. However, among studies of AL, adherence by "verified timely completion" (38.7%–65%) [18,28–29] was lower compared to

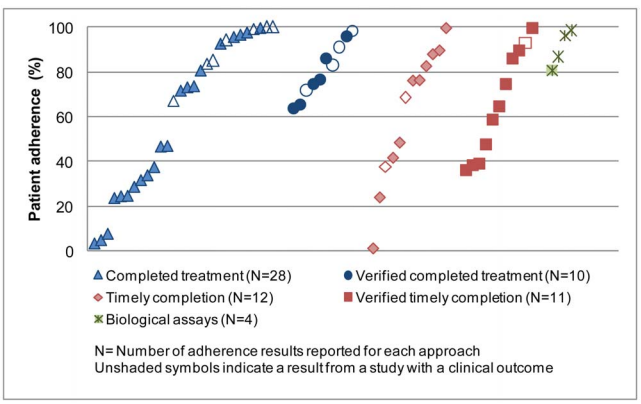

Figure 2. Percentage of patients classified as adherent, by Approach to assessing adherence.

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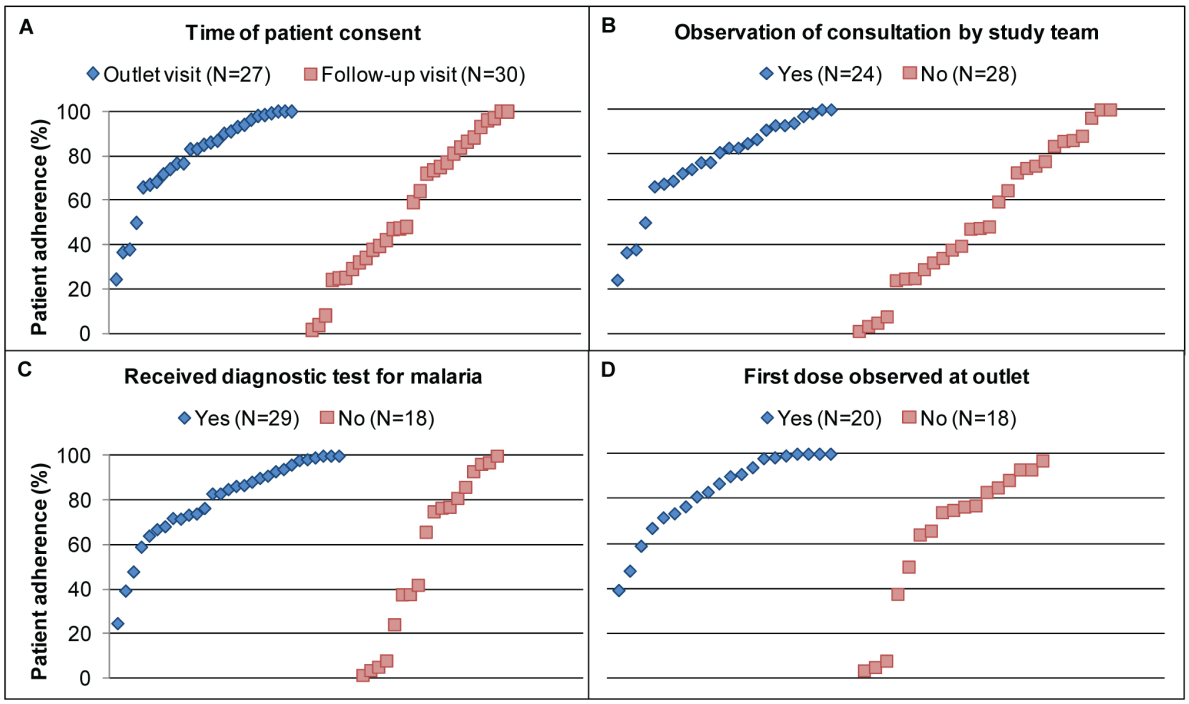

Figure 3. Percentage of patients classified as adherent, by patient interaction with research staff and dispensers.
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"timely completion" (88.3%–100%) [15,22,33], except in studies where the research team enrolled patients at the time the drug was obtained and likely had a more significant research presence than in other studies (90% and 93%) [19,61]. Similarly, adherence to AL by "verified completed treatment" (64.1%–83%) [16,24,27, 29,60] tended to be lower than for "completed treatment" (67%–100%) [22,28,36,38,57–58], with the exception of two household surveys without pill counts with adherence of 47% [41,46].

Household surveys, which all used the "completed treatment" approach and assessed adherence from both public and private community sources, tended to have lower adherence results than studies with other designs, particularly studies with primary clinical outcomes (Tables 1–3). In addition, studies plotted before implementation of an intervention had lower adherence for all approaches, as is particularly evident in the community-based interventions by Marsh *et al.* (1999, 2004) and Winch *et al.* (2003) and the private-sector follow-up study by Denis *et al.* (2008); this may be because most of the interventions included in the review are older studies and the interventions (e.g. pre-packaging of drugs) have become a standard part of antimalarial treatment used in the newer studies.

Among studies using unique approaches, two studies used electronic pill boxes (Medication Events Monitoring Systems – MEMS^{TM}) to measure adherence [34,57]. In the study by Bell *et al.* (2009) adherence by self-report ("completed treatment") was 100% for AL and 99.2% for CPD, but by the electronic pill boxes, adherence was 92% for AL and 91% for CPD. Similarly, in the study by Twagirumukiza *et al.* (2010), adherence to quinine tablets was 100% by both self-report ("verified timely completion") and pill count (no pill boxes had pills remaining), but only 78% of patients took at least 80% of the doses based on the electronic pill box data [34].

Results using biological assays to assess adherence were high (above 90%), but this accounted for only a few studies [15,51,64]. Qingjun *et al.* (1998) evaluated a packaging intervention to improve adherence to chloroquine + primaquine marked with phenobarbital to detect concentrations in plasma, while Na-Bangchang *et al.* (1997) measured adherence to artesunate + mefloquine by whole blood mefloquine concentrations based on a reference interval [64]. Similarly, Congpuong *et al.* (2010) used both whole blood mefloquine concentrations and plasma concentrations of primaquine [63] to detect adherence to artemether + mefloquine + primaquine. One additional study (Shwe *et al.*, 1998) also found high adherence of 99.5%, but was not included in the plots because adherence to artesunate + mefloquine was only reported after implementation of a co-packaging and training intervention; in this study, tablets of quinine and chloroquine were added to the regimen as markers for detection by urine assays. Five other studies measured plasma levels of lumefantrine using HPLC with mass spectrometry or UV detection [19,33,57,60–61], but adherence was not reported on the basis of these assays. Median lumefantrine concentrations were not significantly different between patients who were or were not considered adherent by self-report ("completed treatment" and "timely completion") or self-report with pill count ("verified timely completion").

(ii) Variation by antimalarial type and outlet type

The pattern of adherence results between antimalarials was not clear. Across all approaches and by "completed treatment" adherence to AL (47%–100%) [22,28,36,38,41,46,57–58] was higher than both adherence to monotherapies estimated from

Table 5. Factors associated with adherence in multivariate models ($p<0.05$ or 95% confidence interval crosses the null).

Factors	Studies
Demographics	
Education	
- Caretaker education at least 7 years	Beer et al. 2009 [14]
- Attending some secondary school or beyond	Cohen et al. 2012 [16]
- Higher education	Onyango et al. 2012 [41]
Residence in one of two areas in study location	Duarte et al. 2003 [67]
Age	
- Respondent age 25-50 years versus less than 25 years	Lawford et al. 2011 [27]
- Patient age 15 years or more versus less than 15 years	Lawford et al. 2011 [27]
- Patient age less than 13 years	Onyango et al. 2012 [41]
Ownership of radio	Lemma et al. 2011 [28]
Higher household income	Onyango et al. 2012 [41]
	Simba et al. 2012 [33]
Treatment-seeking behaviour	
Not having sought treatment at a public health facility	Cohen et al. 2012 [16]
Respondent sought treatment within 24 hrs of symptom onset versus waiting longer	Lawford et al. 2011 [27]
Delay of more than 1 day in seeking treatment after the onset of fever	Lemma et al. 2011 [28]
Previous care sought	Souares et al. 2008 [65]
Factors related to the consultation	
Having received exact number of pills to complete treatment	Beer et al. 2009 [14]
Reporting having been given instructions at the shop	Cohen et al. 2012 [16]
Reporting that instructions given were clear	Cohen et al. 2012 [16]
Attended Migowi HC (one of three study outlets)	Mace et al. 2011 [29]
Package used as visual aid by dispenser to explain how to take the drug	Mace et al. 2011 [29]
Received written instructions	Pereira et al. 2011 [31]
Quality of history taking (i.e. nurses at the consultation asked questions about history, symptoms, and previous care)	Souares et al. 2008 [65]
Behaviour	
Took first AL dose at HC	Mace et al. 2011 [29]
Taking AL with food or oil	Simba et al. 2012 [33]
Knowledge and perceptions	
Knowledge that only mosquitoes cause malaria	Gerstl et al. 2010 [20]
Knowledge of malaria aetiology	Khantikul et al. 2009 [25]
Respondent had seen the drug before	Lawford et al. 2011 [27]
Being able to cite at least one correct instruction on how to take AL	Lawford et al. 2011 [27]
Belief that malaria cannot be treated traditionally	Lemma et al. 2011 [28]
Access to information about antimalarials	Khantikul et al. 2009 [25]
Knowledge of the seriousness of the infection/knowing the species in mixed transmission areas	Yepez et al. 2000 [66]
Satisfaction	
Having an improved condition at follow-up	Cohen et al. 2012 [16]
Lower expectation of getting malaria in the next 30 days	Cohen et al. 2012 [16]
Did not report dislikes/side-effects to medication	Lawford et al. 2011 [27]
Preference for AL	Mace et al. 2011 [29]
Satisfaction with received information	Souares et al. 2008 [65]

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household surveys (3.7%–34%) [35,39–40,42,48–49] and adherence to longer primaquine regimens for the treatment of vivax malaria (25%–85%) [21,25,31–32,51,62,66–67]. Adherence to AL by "verified completed treatment" (64.1%–83%) [16,24,27,29,60] was lower than adherence to artesunate-amodiaquine (77%–91%) [14,60] and chloroquine+SP (96%) [26]. However, adherence to AL by "timely completion" was high in three studies (88.3%–100%) [15,22,33] in contrast with studies of SP + amodiaquine (37.7%) [65] and SP + artesunate (76.6%) [23]. By "verified timely completion" adherence to AL was similar in three studies (38.7%–

Table 6. Factors associated with non-adherence in multivariate models ($p<0.05$ or 95% confidence interval crosses the null).

Factors	Studies
Demographics	
Being male	Achan et al. 2009 [56]
	Pereira et al. 2011 [31]
Caretaker having different mother tongue to pharmacist	Depoortere et al. 2004 [17]
Education	
- Caretaker education (none versus some)	Depoortere et al. 2004 [17]
- Lack of formal education	Fogg et al.2004 [19]
Age	
- Being a child under 5	Mace et al. 2011 [29]
- Being a child age 8–10 years versus 2–4 years	Souares et al. 2008 [65]
Head of household profession (retailer/employee vs. farmer)	Souares et al. 2008 [65]
Treatment-seeking behaviour	
No fever reported	Kalyango et al. 2013[1] [24]
Seeking care after 2 or more days	Kalyango et al. 2013[1] [24]
	Takeuchi et al. 2009[2] [62]
Factors related to the consultation	
Treatment with oral quinine versus AL	Achan et al. 2009 [56]
Being counselled about what to do in case of vomiting	Kachur et al. 2004 [23]
Not understanding instructions	Kalyango et al. 2013[1] [24]
Knowledge and perceptions	
Caregiver's perception that illness is not severe	Kalyango et al. 2013[1] [24]
Satisfaction	
Vomiting	Achan et al. 2009 [56]
	Kalyango et al. 2013[1] [24]

[1]Includes patients receiving Al only and AL plus antibiotics (treatment group not significant in multivariate analysis);
[2]Associated with non-adherence in the second week of primaquine treatment for *P. vivax* infection.
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65%) [18,28–29] to adherence to other ACTs (39.4%–75%) [17,20,23] and higher in two other studies (90%–93%) [19,61].

Although most studies evaluated adherence to antimalarials obtained in the public sector, the two descriptive private sector follow-up studies had low adherence, with Nshakira *et al.* (2002) reporting adherence of 37.8% to chloroquine by "completed treatment", and Cohen *et al.* (2012) describing adherence of 65.8% to AL. Three household surveys [46,48–49] and one follow-up study [45] assessing interventions in private drug stores and surrounding communities also all reported adherence of less than 50%. Adherence where antimalarials were obtained from CHWs in four studies using follow-up methods ranged widely from 1.5%–100% [15,24,28,54], with a study of AL by Lemma *et al.*(2011) in Ethiopia finding adherence of 38.7% by "verified timely completion" and 73.5% by "completed treatment". In addition, a study evaluating adherence to ACTs dispensed by CHWs reported high adherence of 83%–97% by "completed treatment" in household surveys in three countries [36].

(iii) Variation by nature of interaction of patients with dispensers and research personnel

We explored how adherence results varied depending on the nature of the interaction reported between patients and their dispensers, and between patients and research personnel. Figure 3a–d shows how patient adherence (as assessed by any of the five approaches) varied with four aspects of patient interaction that we hypothesised might influence adherence results. As shown in the first plot, patients in some studies were asked for informed consent to participate in the study at the outlet upon obtaining the drug, while patients in other studies were not asked for informed consent until a later follow-up visit, having had several days to take the drug (Figure 3a). Secondly, research staff in some studies observed the consultation of the patient with the dispenser or conducted the consultation themselves, while other studies did not (Figure 3b). Studies where most patients obtained a malaria diagnostic test prior to treatment were plotted in comparison to studies where patients were not tested (Figure 3c). The fourth plot compares studies where dispensers did and did not observe the patient swallowing the first dose of the drug (Figure 3d). Results of all studies that used one of the five approaches are plotted, as described previously for Figure 2, except that for studies using multiple approaches to assess adherence, only the most inclusive approach reported was plotted (i.e. "completed treatment"). Studies could not be plotted if the nature of the patient interaction for each of the four plots was not reported.

Figure 3a suggests that collecting informed consent from patients at the outlet visit when the drug is dispensed can result in higher adherence compared to requesting informed consent at the time of the follow-up visit. Similarly there is an indication that observation by the study team of patients' consultations with dispensers may influence patients to be more adherent (Figure 3b), and that where patients were confirmed to have malaria with a

rapid diagnostic test (RDT) or blood smear prior to being dispensed antimalarials, adherence was higher than among those not tested (Figure 3c). There is also some indication that studies where dispensers observed patients' first dose had higher adherence than those where the first dose was not observed, although the pattern is less clear (Figure 3d).

(iv) Factors associated with adherence in multivariate models

Understanding the characteristics and behaviours associated with patient adherence to antimalarials is vital to designing interventions to improve appropriate use of ACTs. Twenty-four studies used multivariate analysis to examine factors associated with adherence: of these, 13 studies reported 30 factors significantly associated with adherence in multivariate models, nine studies found 12 factors associated with non-adherence, and five studies reported not finding any factors significantly associated with adherence or non-adherence [32,44,50,55,61]. While many of the twenty-four studies tested similar factors, such as demographics, instructions given and patient knowledge, there was substantial diversity in which factors were found significant.

Tables 5–6 show factors significantly associated with adherence (Table 5) and non-adherence (Table 6), including demographics, treatment-seeking behaviour, factors related to the consultation, behaviour, knowledge and perceptions, and satisfaction. Factors significantly associated with adherence in more than one study included higher education [14,16,41], higher household income [33,41], provision of better information on how to take drugs [16,29,31], and knowledge about malaria and antimalarials [20,25,27–28,66]. Factors significantly associated with non-adherence in more than one study included being male [31,56], lack of education [17,19], and vomiting [24,56]. There were contrasting results for the effects on adherence of patient age and the number of days after onset of symptoms that treatment was sought. Older age of the patient was associated with adherence in one study [27] and non-adherence in another [65], while two other studies found younger age associated with adherence [41] and non-adherence [29]. Similarly, Lemma *et al.* (2011) found that patients who waited more than one day to seek care after onset of fever were more likely to be adherent, but other studies showed that seeking care within 24 hours of symptom onset was associated with adherence [27], and waiting two or more days was associated with non-adherence [24,62].

Discussion

Extensive variation was observed in patient adherence to antimalarials, with many studies reporting very high adherence (90–100%) and others finding clearly suboptimal adherence, sometimes of less than 50%. This may be an important problem, both in terms of clinical outcomes and also in the context of the development of resistance to artemisinin in South-East Asia [68]. However, it is unclear how good adherence must be for ACTs to be efficacious, and which features of adherence (such as correct timing of dose intervals or taking each dose with a fatty meal) matter most.

We identified five overarching approaches to assessing adherence based on recall ("completed treatment" and "timely completion"), recall and pill counts ("verified completed treatment" and "verified timely completion") and on biological assays. By "completed treatment" and "verified completed treatment", adherent patients were defined as completing the full course of treatment though not necessarily following a specific schedule. Whether these are appropriate approaches to assess adherence should be considered in light of the pharmacology of the specific drug: if the safety or efficacy of the drug is critically dependent on the timing of the doses then it will be important to assess this when evaluating adherence. As these approaches do not include the spacing of the doses, it is possible for patients to have taken some doses too close together or even to have taken all doses at one time and still be considered "adherent", though such practices could be of concern for drug safety and efficacy. Furthermore, there is potential variation within each approach in what was considered correct treatment, with some studies taking into account national guidelines on the correct dose-for-weight that the patient should have consumed and other studies assuming the correct amount was obtained.

By "timely completion" and "verified timely completion", adherent patients were defined as exactly following instructions in terms of dose, frequency and duration according to their responses to interview questions. As noted above, there was considerable variation in definitions of "correct" timing, which may have affected comparability within these approaches. More information is needed on how precise time intervals between doses must be in order for drugs to be efficacious. For example, the packaging of various brands of AL states that the second dose should be taken eight hours after the first dose, which would fall in the middle of the night if the drug is obtained in the evening. In this situation it is unclear whether a patient should still be considered adherent if they take the drugs first thing the next morning instead.

The majority of the adherence studies used one or more of these approaches relying primarily on self-reported drug histories, which may be susceptible to recall and social desirability bias. Studies in Tanzania and Cambodia found high levels of antimalarials circulating in the blood among patients stating they had not taken any drugs in the previous 28 days [69–70]. Patients may not accurately recall information about the quantity of drugs taken. Moreover, even if the precise time of obtaining the drug from the provider is known, asking patients when each dose was taken is problematic as they may not have had clocks available or may not know or remember the exact time. Recall bias is likely to be higher in data obtained from household surveys, where interviewers frequently ask about drugs taken in the previous 14 days, compared to follow-up studies, where recall time is usually 4–7 days. Even with short recall periods, patients may not correctly remember details related to each dose. Cultural and demographic factors may also affect the reliability of self-reported data [71]. For example, in a study of the impact of the length of recall periods for health surveys, different recall periods gave different results, and these differences were shown to vary by income group [72].

To avoid being seen as ignorant or negligent, patients who are aware of the expected behaviour may say they were adherent even if they actually were not. A study by Peeters Grietens *et al.* (2010) found that while 72% of patients reported taking the full course of primaquine, only 49% claiming to take the full course had actually received the full course according to records [21]. Likewise, Bell and colleagues stated that self-reported data, which resulted in 100% adherence to AL and CPD in Malawi, was unreliable compared to MEMS^{TM} containers [57].

In order to reduce recall and social desirability bias, some studies incorporated manual examination of drug packaging into their definitions of adherence ("verified completed treatment" and "verified timely completion"). For studies of AL, these approaches yielded lower adherence results than the equivalent approaches without the pill counts ("completed treatment" and "timely completion"). However, even results including pill counts may over-estimate true adherence as removing pills from blister packs does not guarantee that the pills were consumed. Similarly, opening electronic pill boxes does not guarantee a dose was

consumed. Patients may have "played" with their pill boxes, opening them without removing pills, or alternatively, they may also have removed multiple doses at one opening, either to discard, consume, or save until the appropriate time.

Despite the limitations of self-reported and pill count approaches, Souares *et al.* (2008) suggested that self-reported data may be more reliable and feasible than assays for drug levels, which require invasive sample collection and complicated field logistics [68]. Drug assays were rarely used for measuring adherence, and their utility and appropriate role remains unclear. Adherence evaluated by the detection of drugs in biological assays was very high (90–100%) in four studies, but these studies assessed adherence to drugs other than AL and involved close interaction of the research staff with patients and in some cases extended follow-up periods. The five studies that reported measuring lumefantrine concentrations, but did not incorporate these assays into adherence results, did not find significant differences in lumefantrine concentrations between patients adherent and non-adherent by self-report. This may have been due to the metabolic variability of the study population, including age, pregnancy, concomitant fat intake and other factors affecting drug absorption, limiting the value of quantitative assessments of patient adherence [73–74]. Methods of collecting blood samples, sample preservation under field conditions, and details of the assays themselves are also likely to affect results.

Regardless of the approach used for assessing adherence, Hawthorne bias may occur if a patient's awareness of being studied positively influences medication-taking behaviour. Similarly, if researchers observe patient consultations with the dispenser, this may positively influence the care and advice provided by the dispenser and/or patients' attentiveness and adherence to the treatment. In the studies reviewed here, adherence was higher when informed consent was collected at the time of obtaining the drug and to some degree when patient consultations were directly observed (Figures 3a and 3b). While it is reasonable to assume that medication-taking behaviour of patients who are not aware they are being studied more accurately reflects behaviour in real life contexts, these concerns must be balanced by practical constraints, such as fulfilling other study objectives and the need to obtain the patient's consent and address for follow-up visits.

Some specific patient-dispenser interactions might also be expected to improve adherence. For example, confirmation of diagnosis of malaria by an RDT or blood smear might increase adherence if patients are more aware that they are suffering from malaria, and if patients with confirmed malaria see a better response to treatment than those who have other conditions. Observing the first dose of treatment is another commonly recommended practice and was found to be significantly associated with adherence to AL in one study [29]. We found some indication that malaria diagnosis was associated with higher adherence in the reviewed studies, although the effect was less marked for observing the first dose on adherence overall.

In addition to the approach to measurement and the nature of the patients' consultations, other factors often hypothesised to influence adherence include patient characteristics, antimalarial type and outlet type. However, it was not possible to discern clear patterns across the studies reviewed. There was some evidence from multivariate studies that patients who had higher socio-economic status and were better educated or informed had higher adherence. While there is some concern that the greater number of tablets required for treatment with ACTs (i.e. 24 for an adult) contributes to lower adherence compared to antimalarials requiring fewer tablets, this was not clear in the studies reviewed here. One potential explanation for this is that ACTs often come in co-formulated or co-packaged blister packs, with different coloured packages for each age or weight group. This is in contrast to loose tablets dispensed into paper envelopes, which was often the case for older antimalarials. Not only can the dispenser give the patient the incorrect number of tablets, but the tablets may need to be cut in half to achieve the appropriate doses, and it may be more difficult for the patient to remember how many to take. Secondly, more effective antimalarials such as ACTs may encourage higher patient adherence; if drugs are perceived to be ineffective, patients may use a drug briefly or not at all before looking for a more effective alternative [8]. Finally, perceptions of side-effects may cause variation in adherence across antimalarials, with drugs such as chloroquine and quinine known to have more common minor adverse effects than ACTs such as AL.

It was hard to assess variation across outlet types as of the 55 studies included, only five specifically evaluated adherence to antimalarials from private drug shops [16,30,45,48–49] and five from community health workers [15,24,28,36,54]. However, there were some indications that adherence was relatively low from private sector outlets, highlighting the need for more studies to evaluate adherence to ACTs obtained in this sector and to design interventions to ensure drugs are used appropriately. Interventions to improve adherence that are currently being tested in the private sector include the introduction of RDTs [75–76], new packaging, SMS reminders to patients [77], and SMS reminders to drug shop dispensers to encourage them to advise patients on the importance of adherence [78].

Conclusion

The literature reports extensive variation in patient adherence to antimalarials. The unsatisfactory patient adherence sometimes reported to ACTs obtained in the public sector, and the current dearth of data from the private sector, represent significant challenges for maximising the impact of ACTs. Variations in adherence may reflect factors related to patient characteristics and knowledge, their treatment seeking behaviour, and the nature of their consultation with the provider. However, methodological variations between studies are also likely to be an important source of variability in results, including the methods used for collecting data, and any interaction between the research team and patients before and during the treatment course. Future studies could be strengthened by a greater awareness of the impact of study procedures on adherence outcomes, and the identification of improved measurement methods that are less dependent on self-report.

Supporting Information

Checklist S1 PRISMA checklist.
(DOC)

Flow Diagram S1 PRISMA flow diagram.
(DOC)

Author Contributions

Conceived and designed the experiments: KB CG SPK DS. Performed the experiments: KB. Analyzed the data: KB. Contributed reagents/materials/analysis tools: KB CG SPK DS. Wrote the paper: KB CG SPK DS. Conceived and designed the review: KB CG SPK DS. Conducted the literature search: KB. Abstracted the data: KB. Analyzed results: KB. Wrote the first draft of the paper, with inputs from all authors: KB. Read and approved the final paper: KB CG SPK DS.

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2.3 Updates to the literature review paper

In addition to our published review, two other related reviews were also published in January 2014. First, the review by Fuangchang *et al.* focused on interventions to improve adherence to antimalarial drugs [1]. The authors identified 16 studies, though some of the studies included under the categories of medication supervision and convenient regimen were trials assessing effectiveness of supervised versus unsupervised treatment (n=2 studies) or comparing effectiveness of drugs (n=4 studies) and were not actually interventions to improve adherence. The authors categorised interventions into six types: packaging aids, visual media, combined visual media and verbal information, community education, medication supervision, and convenient regimen. The most effective approach for improving adherence was suggested to be the combination of visual media and verbal instructions, although this was based on limited evidence. Similar to our review, the authors noted that some effective interventions, such as pre-packaging, are now standard for ACTs, and that there are relatively few studies assessing interventions to improve adherence to ACTs, particularly in the private sector.

The systematic review by Banek *et al.* [2] focused on ACTs, and compared levels of adherence by ACT regimen, noting as we do that factors such as study designs, definitions, and methods of assessing adherence vary substantially. In distinction, our review included studies of all antimalarial drugs, compared results of studies using different approaches to assessing adherence, and examined the effects on adherence of patient interaction with research staff and dispensers. Echoing the 2005 review by Yeung and White [3], both our review and the Banek *et al.* review emphasise the need for improved and standardised methods of assessing adherence.

Through reading the Banek *et al.* review and personal communication with the lead author, I became aware of eight studies that were erroneously omitted from our review. There were several

reasons for these omissions. First, I systematically searched only one database (PubMed), using fairly general search terms ((Medication Adherence (MeSH) or Patient Compliance (MeSH) or compliance or adhere*) and (Antimalarials (MeSH) or antimalarial*)). In contrast, Banek *et al.* searched three databases (Medline, Embase, and Global Health) with comprehensive search terms that included many of the common names used for each available antimalarial drug. Had I searched the Global Health database or possibly used different search terms, I would have identified additional studies [4-8]. Secondly, I conducted the search alone, reading a large number of abstracts and manuscripts. In doing so, I overlooked several studies that were in my search results [9-11]. Having a second reviewer to compare findings with might have prevented these studies from being inappropriately excluded.

Table 2.3.1 contains the details of the studies that were missed in our published review, as well as four new studies that were published after January 2013, when our search was completed and through September 2014, when the table was updated [12-15]. These studies have been added to the plots of the percentages of patients classified as adherent, by patient interaction with research staff and dispensers (Figure 2.3.1). As in our published review, studies that did not use one of the five approaches to assess adherence were not plotted. For studies using multiple approaches, only the most inclusive approach was plotted (e.g. “completed treatment”). In addition, when results of adherence to the same drug were reported from more than one study site within the same country, the weighted average of these sites was plotted. For intervention studies, only baseline or control results were plotted in order to represent standard practice. Thus, five of the eight missed studies and two of the four new studies were added to the plots.

Table 2.3.1 Characteristics of additional studies meeting criteria for inclusion in review (through September 2014)

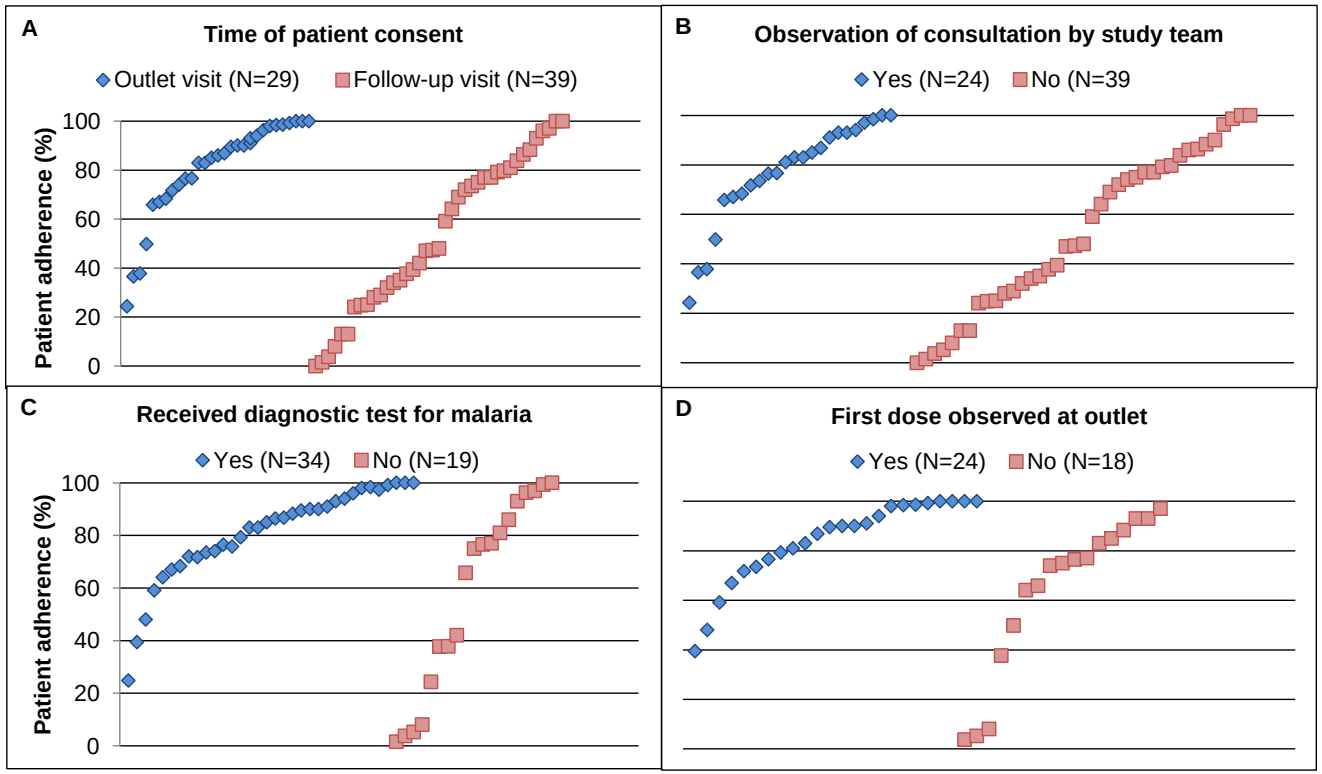
Study **Country** **Type of study** **Source(s) of drugs**	**Drug regimen(s)**[1,2]	**Method(s) of assessing adherence**	**Approach(es) to assessing adherence**[3]	**Day of follow-up visit (Day 1 = drug dispensed)**	**Level of adherence (N=denominator)**	**Other notes**
Alba et al. 2010 [7] Tanzania Descriptive Multiple sources	AL, SP	Household survey questionnaire	Completed treatment	n/a	SP (2004): 76% (N=72) SP (2008): 84% (N=49) AL (2008): 69% (N=32)	Plotted, weighted average for SP
Almeida et al. 2014 [12] Brazil Descriptive Health facility	Chloroquine + primaquine (7 days)	Self-report (compared dichotomous scale (DS) to six-point Likert scale (LS)), pill count	*Unique approach (1) =* based on scores to DS and LS, with values below the median used to determine adherence *Unique approach (2) =* pill count only with 70% of pills taken used as adherence cut-off	Day 8	*Unique approach (1):* 68.9% (N=135) *Unique approach (2):* 71.1% (N=135)	Not plotted (unique approach)
Asante et al. 2009 [8] Ghana Clinical Health facilities	Artesunate + amodiaquine (3 days)	Pill-count	*Unique approach =* correct number of pills remaining	Day 3	92.6% (N=211)	Not plotted (unique approach)
Meankaew et al. 2010 [6] Thailand Intervention Health facilities	Artesunate + mefloquine (AS + MQ) (3 days) Chloroquine + primaquine (CQ + PQ) (14 days)	Self-report	Completed treatment	Day 7 (ASMQ) *Or* Day 14 (CQ + PQ)	*No intervention: n/a* *With intervention:* AS + MQ: 94% (N=285) CQ + PQ: 42.6% (N=249)	Mobile technology module for malaria disease and treatment monitoring Not plotted (with intervention only)
Minzi et al. 2014 [13] Tanzania Descriptive Health facility	AL (3 days)	Self-report, pill count, laboratory assays[4]	Completed treatment, Verified timely completion	Day 4	Completed treatment: 79.7% (N=143) Verified timely completion: 7% (N=143)	Plotted most lenient approach only (completed treatment)

Study **Country** **Type of study** **Source(s) of drugs**	**Drug regimen(s)[1,2]**	**Method(s) of assessing adherence**	**Approach(es) to assessing adherence[3]**	**Day of follow-up visit (Day 1 = drug dispensed)**	**Level of adherence (N=denominator)**	**Other notes**
Mubi et al. 2011 [10] Tanzania Descriptive Community health workers	AL (3 days)	Self-report	Timely completion	Day 4	AL (clinical diagnosis group): 99.3% (N=1399) AL (RDT group): 97.4% (N=760)	RCT comparing clinical diagnosis with rapid diagnostic tests Plotted, weighted average except for diagnosis plot
Ogolla et al. 2013 [15] Kenya Descriptive Health facility	AL (3 days)	Self-report, pill count	Verified timely completion	Day 4 (?)	75.8% (N=62)	Minimal information given in text, plotted when data available
Ogutu et al. 2014 [14] Kenya Clinical Health facility	AL (3 days), dihydroartemisinin-piperaquine (DHAPQ) (3 days)	Unclear	Unclear	n/a	AL: 93.6% (N=126) DHAPQ: 85.6% (N=124)	All patients admitted until clinically stable with a negative blood slide. Interviewed on discharge and at subsequent follow up visits. Unclear how adherence was measured, or if this study meets inclusion criteria, therefore not plotted.
Ratsimbasoa et al. 2012 [11] Madagascar Clinical Community health workers	Artesunate-amodiaquine (3 days)	Self-report, pill count	Verified timely completion	Day 4	90% (N=543)	Plotted

Study **Country** **Type of study** **Source(s) of drugs**	**Drug regimen(s)**[1,2]	**Method(s) of assessing adherence**	**Approach(es) to assessing adherence**[3]	**Day of follow-up visit (Day 1 = drug dispensed)**	**Level of adherence (N=denominator)**	**Other notes**
Watsierah et al. 2011 [9] Kenya Descriptive Multiple sources	AL, SP, quinine (QN), chloroquine (CQ)	Household survey questionnaire	*Unique approach (1)* = correct dose *Unique approach (2)* = correct duration	n/a	*Unique approach (1):* AL: 29.4% (N=127) AP: 85% (N=147) QN: n/a CQ: 51.7% (N=29) *Unique approach (2):* AL: 33% (N=127) SP: 82% (147) QN: 96.4% (28) CQ: 34.5% (29)	Not plotted (unique approaches)
Yeung et al. 2008 [5] Cambodia Descriptive Multiple sources	Artesunate + mefloquine (AS + MQ), other ACT, artesunate monotherapy (AS), quinine + tetracycline (QN + tet), quinine (QN), choloroquine (CQ)	Household survey questionnaire	Completed treatment	n/a	AS + MQ: 77% (N=44) Other ACT: 13% (N=31) AS: 28% (N=29) QN + tet: 0% (N=13) QN: 13% (N=24) CQ: 35% (N=63)	Plotted (all of results as different drugs)
Zaw Win et al. 2012 [4] Myanmar Descriptive Health facilities	AL (3 days)	Self-report, pill count	Verified completed treatment	Day 4	89.5% (N=248)	Plotted

[1] Duration of drug regimen in days not given for household surveys.
[2] Co-formulated combination therapies are written with a "+", as opposed to a "-" (not co-formulated).
[3] See Table 4 in published review for definitions.
[4] Not incorporated into adherence definition.

Figure 2.3.1 Percentage of patients classified as adherent, by patient interaction with research staff and dispensers (updated)



N= Number of adherence results reported from studies with this characteristic
Number of studies not reporting data: 2 (A), 7 (B), 11 (C), 21 (D)

In both the studies in the published review and those in Table 2.3.1, the diversity of study drugs, settings, and factors related to study design made it difficult to identify any differences in adherence among approaches involving exact timing of doses compared to completion of treatment, or compared to studies where these approaches were verified by pill counts. Among studies of AL, however, some trends were apparent, and incorporating the studies in Table 2.3.1 had an effect on the ranges of results for approaches with and without pill count. Our published review suggested that "verified completed treatment" (64.1%-83%), was lower compared to "completed treatment" (67%-100%) and "verified timely completion" (38.7%-65%) was lower compared to "timely completion" (88.3%-100%). Incorporating the studies in Table 2.3.1 changed the range of "verified completed treatment" from 64.1%-83% to 64.1%-89% [4, 16-20] , but did not change the range for "completed treatment" ((67%-100%) [13, 21-26], (47%-100% if household surveys are included [7, 27, 28]). The range for "verified timely completion" changed to 7%-75.8% [13, 15, 18, 26, 29] (7%-93% if including three studies where the research team enrolled patients at the time the drug was obtained and likely had a more significant research presence than in other studies [11, 30, 31]), but the range for "timely completion" did not change (88.3%-100%) [10, 25, 32, 33]. Consequently, there is now less suggestion in the literature that studies using pill count in addition to self-report to assess completion of AL treatment had lower results than if self-report alone was used, but there is some indication that in studies of AL with minimal involvement from the research team, timely completion was lower when pill counts were used along with self-report. However, other factors related to study context and methodologies may also affect these results.

Consistent with our published review, Figure 2.3.1 demonstrates that patient interaction with research staff and dispensers may influence adherence. Higher adherence was observed in studies (A) where informed consent from patients was collected at the consultation (when the drug was dispensed) compared to at the time of the follow-up visit, (B) where the study team observed patients'

consultations with dispensers, (C) where patients were confirmed with a diagnostic test to have malaria, and (D) where dispensers observed patients taking the first dose of treatment. While the number and characteristics of studies with information available may affect the trends observed in these plots, and the plotted interactions may also be interrelated (e.g. studies with higher research staff involvement might have also required confirmation of malaria and observation of the first dose), these results suggest that future adherence studies should minimise patient interaction with research staff in order to avoid bias. In terms of policy, testing for malaria and observation of the first dose of treatment are good practices that might encourage patient adherence.

Our published literature review explored factors associated with adherence or non-adherence in multivariate analyses, finding that these associations varied considerably between studies. There was some evidence that patients who had higher socioeconomic status and were better educated or informed had higher adherence, although as Banek *et al.* note, these associations were not consistent across studies. Among the studies in Table 2.3.1, only three report examining factors associated with adherence or non-adherence in multivariate analyses. Minzi *et al.* did not find age, sex, or education associated with adherence, but found that the odds of adherence were much higher among patients taking the first dose at the health facility compared to those who took the first dose at home [13]. In the household survey by Yeung *et al.* adherence was similarly not affected by age, sex, education, socioeconomic status, or distance from closest public health facility [5]. Finally, Watsierah *et al.* reported that knowledge of antimalarial drugs was associated with taking the correct dose and taking the drug for the correct duration [9].

In summary, this section updates our literature review publication with additional studies from two other reviews and several new studies. Overall, the main conclusions of our published review are upheld and supported by the additional studies, though the evidence that using pill counts in addition to self-report leads to lower estimates of adherence was slightly weakened.

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3 Research Context

This chapter describes the context of the research presented in this thesis. Section 3.1 begins by describing the geography and sociodemographics of Tanzania, trends in mortality rates, and malaria epidemiology. Options for malaria treatment in the public and private retail sector are explained. Section 3.2 focuses on Mtwara, the region where the studies took place. Finally, Section 3.3 outlines the IMPACT2 project, the umbrella project under which this thesis was developed.

3.1 Tanzania

Tanzania is a large country in East Africa, sharing borders with Kenya, Uganda, the Democratic Republic of Congo, Rwanda, Burundi, Zambia, and Mozambique (Figure 1). The country is divided into 30 administrative regions, with a population in 2012 of 44,928,923 [1], including mainland Tanzania and the islands of Zanzibar. Seventy percent of Tanzanians live in rural areas, and over half of the population is under 18 years of age. Tanzania is among the least developed countries in the world, ranking 159th among 187 countries in the 2013 Human Development Index [2]. Gross national income per capita is $630, 43.5% live on less than $1.25 per day, and 28% are below the national poverty line [3]. Net enrolment in primary school for children aged 7-13 years is approximately 77%, with little difference between males and females, and the adult literacy rate is 78% (2012) [1]. Secondary school enrolment for children aged 14-19 years is much lower (25.3% in 2010, data not available for 2012) [4].

Tanzania has made progress in recent years at reducing mortality rates. Between 2006-2010, mortality among children under five years was 81 deaths per 1,000 live births, compared to 106 and 143 deaths per 1,000 live births from 2001-2005 and from 1996-2000, respectively [4]. Similarly, in the last decade infant mortality has declined by 50%, but improvements in neonatal mortality are not as substantial, decreasing from 33 deaths per 1,000 live births from 1996-2000 to 26 deaths per 1,000 live

births from 2006-2010. Maternal mortality has also remained a challenge, with 432 deaths per 100,000 live births in 2012 [1, 4].

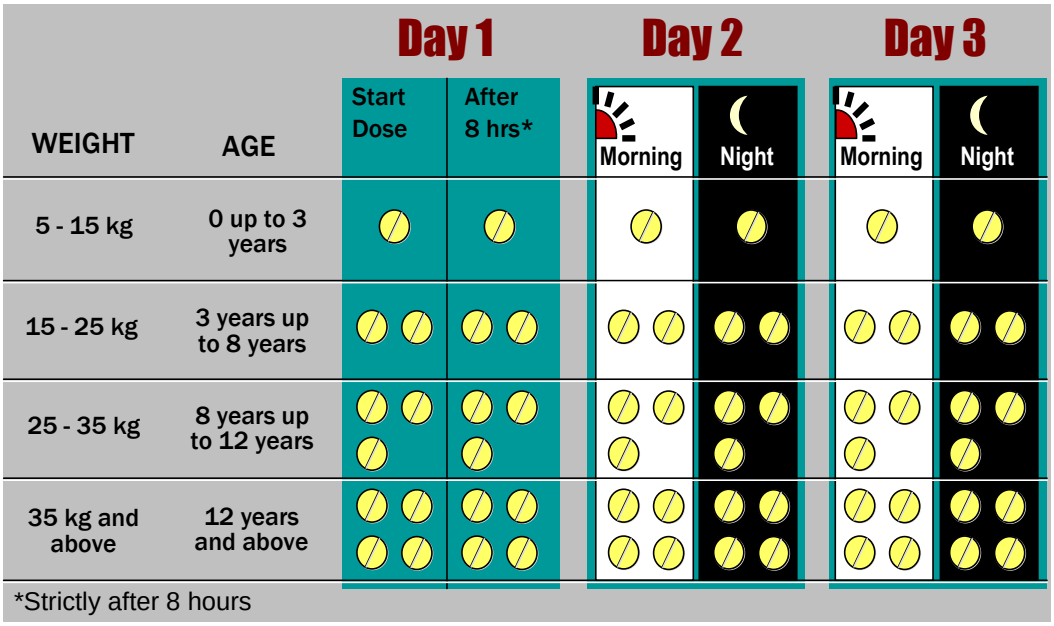
Figure 1: Map of Tanzania showing zonal and regional boundaries. (Source: Tanzania HIV / AIDS and Malaria Indicator Survey, 2011-2012 [5])

Malaria continues to be a leading cause of morbidity and mortality in mainland Tanzania, where 100% of the population is considered at risk. In 2012, there were approximately 40 confirmed cases per 1000 population and 15 inpatient deaths per 100,000 [6]. The major species is *P. falciparum*, with very few infections caused by *P. malariae* and *P. ovale*, and the principal vectors are the *Anopheles gambiae*

complex (*An. gambiae s.s* and *An. arabiensis*). Seasonal malaria corresponds with the main rainy season, typically from March-May, with some parts of the country also experiencing rain November-January. In the largely arid central plateau, malaria is unstable and seasonal, while higher year-round transmission with some seasonal variations occurs in regions along the coast, Lake Victoria, and the southern lowlands. The remainder of the country has stable, seasonal transmission. Prevalence of malaria has been declining in much of the country, with 18% of children age 6-59 months positive by RDT in the 2007-2008 Tanzania HIV and Malaria Indicator Survey (THMIS) [7], compared with 9.5% in the 2011-2012 THMIS [5]. Prevalence is highest around Lake Victoria and in the southern lowlands.

In Tanzania, treatment for malaria is sought from public health facilities, private not-for-profit facilities, and private for-profit outlets. Public health facilities include hospitals, health centres, and smaller dispensaries. According to national guidelines, treatment for malaria is provided free of charge for children under five years, pregnant women, the elderly, and those who cannot afford to pay [8], but these exemptions are not always implemented [9, 10]. Tanzania adopted AL as the first-line antimalarial drug in 2004, although it was not available in public health facilities until 2006. The recommended treatment regimen is six doses over 3 days, with 1-4 tablets (20 mg artemether / 120 mg lumefantrine) per dose depending on the patient's weight / age band (Figure 2). Dispersible tablets are used for children. National guidelines state that the second dose should be taken eight hours after the first dose, followed by the remaining doses each morning and evening of the second and third days [11]. To maintain stocks of AL, drugs are ordered through an Integrated Logistics System (ILS), in which individual health facilities submit requests to the District Medical Officer (DMO), who then authorises drugs to be delivered from zonal stores. Health workers also receive text message prompts to report on current stocks from the *SMS for Life* system, which records data on drug stocks in each health facility and sends summary reports to the DMO [12].

Figure 2: Example of AL treatment regimen (Source: Tanzania National Guidelines for Diagnosis and Treatment of Malaria, 2011 [11])



Diagnosis of malaria was mostly presumptive in health facilities until RDTs were rolled out in 2010-2012. However, an evaluation in three regions (Mwanza, Mbeya, and Mtwara) in 2012 showed that only about half of febrile patients attending public health facilities were tested, and facility stock-outs of both RDTs and AL were major challenges [13]. Stock-outs in the public sector were suggested to be one reason for a shift in care-seeking behaviour from public health facilities to the private retail sector observed in rural areas in a household survey in these regions from 2010-2012 [14]. Across all health facilities in Tanzania during a 15-month period from October 2011-December 2012, complete stock-outs of all four packs of AL were recorded from an average of 29% of health facilities each week [15].

In the private for-profit sector, treatment for malaria in Tanzania is frequently obtained from private facilities and the private retail sector (pharmacies, drugs stores, and general shops). As pharmacies are typically not located outside of urban centres, the 9,000-plus drug stores account for the

majority of private retail sector sales in peri-urban and rural areas. Prior to 2003, the primary drug stores were *duka la dawa baridi* (DLDB). These shops were typically small buildings with cement or brick walls and a tin roof [16]. Most shops had 1-2 sellers with a low-level medical qualification (e.g. nurse assistant) and less medical training than the required four years. They were allowed to stock over-the-counter medicines, such as antipyretics / pain killers and oral antimalarials (e.g. chloroquine, amodiaquine, and SP), but not prescription-only antimalarials (e.g. injectables) and oral antibiotics. However, many DLDB illicitly stocked unregistered or prescription-only drugs [16-18]. Drugs were mostly obtained from wholesalers or pharmacies in Dar es Salaam, although many shops were located several hundred kilometres away. DLDB were required to be registered with the Tanzania Food and Drug Administration (TFDA), but knowledge of regulations was poor and many shops failed to obtain the appropriate permits. Furthermore, TFDA funding for inspections was very limited, and DLDB were essentially able to operate outside of the regulatory framework [18].

In 2001, the Strategies for Enhancing Access to Medicines (SEAM) Program run by Management Sciences for Health (MSH) through a grant from the Bill and Melinda Gates Foundation conducted an assessment that identified many of these issues. The Accredited Drug Dispensing Outlets (ADDO) initiative was launched by TFDA and SEAM in order to improve availability, quality, and affordability of pharmaceutical services in rural and peri-urban areas without pharmacies [19]. ADDOs (also known as *duka la dawa muhimu (DLDM)*, or essential drug shops) were first piloted in Ruvuma region in 2003, with a wide range of stakeholders participating in the design and implementation of the program [18].

Upgrading and accreditation of DLDBs to ADDOs involved multiple components. Dispensers were required to have a health qualification of a nurse assistant or higher. A mandatory six-week training included topics such as laws, regulations, record-keeping, and dispenser ethics, as well as ADDO-approved medicines, common indications and contraindications, common dosages, side effects, patient information, and effective communication skills. The intent was for ADDO dispensers

to fill prescriptions, or when prescriptions were not available, to ask about the patients' symptoms, recommend appropriate treatment, provide advice on how to take medicines at home, and when necessary refer patients to health facilities for further care. In addition to training, the ADDO program involved dispenser incentives, including permission to sell an approved list of prescription-only medicines (e.g. certain oral antibiotics and oral quinine), a marketing campaign to raise awareness of ADDOs, and the establishment of regional pharmaceutical wholesalers. To improve regulation, government officials were trained to conduct ADDO inspections several times per year.

By August 2005, more than 150 shops had been accredited, and an evaluation of the ADDO program showed some improvements in access to quality medicines and services [18, 19]. The Ministry of Health and Social Welfare then decided to expand the program nationwide and phase-out DLDBs. Although ACTs were the first-line treatment for uncomplicated malaria and available in public health facilities since 2006, the expense of ACTs ($8-10 in pharmacies) limited their availability in ADDOs [20]. In 2007-2008, a pilot program to make subsidised ACTs available in ADDOs was conducted in five districts each in Ruvuma and Morogoro regions, led by TFDA, the NMCP, and SEAM, with funding from the President's Malaria Initiative (PMI). ACTs were added to the list of prescription-only medicines that ADDOs were allowed to sell, and the pilot program established a supply of subsidised ACTs, set a recommended retail price, and ran a two-day training for dispensers on treatment of malaria with ACTs, as this had not been covered in previous training. After one year of the program, 70% of ADDOs stocked ACTs, and the percentage of antimalarial sales that were ACTs had increased modestly from 3% in July 2007 to 28% in June 2008, with substantial variation by district [21].

Another study run by the Clinton Health Access Initiative (CHAI) also piloted the introduction of subsidised ACTs in regions where ADDOs had not yet been introduced [22]. Dispensers at DLDB in an intervention district in each of Shinyanga and Dodoma regions were trained for one day on malaria symptoms and ACT dispensing and were given permission to sell ACTs. A designated wholesaler in Dar es

Salaam purchased the ACTs at a subsidised price ($0.11) and sold them to DLDB in the intervention districts. Compared to the TFDA pilot in Morogoro and Ruvuma ADDOs, a similar proportion of DLDB stocked ACTs after one year (70%). However, a more marked increase from 1% in August 2007 to 44% in August 2008 was observed in the percentage of antimalarial sales that were ACTs. In addition, the CHAI pilot found that DLDBs that had not stocked ACT during the study were located farther from roads, the district town, other DLDB and public facilities, and had lower total antimalarial sales [23].

Both the TFDA and CHAI studies piloted the provision of subsidised ACTs in drug shops. This approach was subsequently expanded nationwide as Tanzania was one of seven pilot countries (eight considering Zanzibar separately) to receive AMFm-subsidised drugs. The first co-paid drugs for the private for-profit sector arrived in Tanzania in October 2010, and by the end of 2012, nearly 24.6 million doses had been delivered [14]. The Medical Stores Department was the first-line buyer for the public sector, while in the private for-profit sector ten first-line buyers were registered, five of which placed orders with manufacturers. The recommended retail price for an adult dose was 1,000 Tanzanian Shillings ($0.64). Interventions to increase community awareness of subsidised ACTs included mass media campaigns (e.g. TV and radio spots). Community-level communications, such as shows and school activities led by community change agents and community based organisations, took place in two districts per region. The Independent Evaluation showed that AMFm led to significant reductions in the price of ACTs and a corresponding increase in their availability and market share [24]. Availability of quality-assured ACTs increased from 11% to 66% in the private for-profit sector between 2010 and 2011, with their market share increasing from 2% to 32% [14].

Although ACTs were officially only allowed to be sold in ADDOs, AMFm-subsidised ACTs flowed through the normal distribution channels, reaching drug stores in regions with and without ADDOs (Thomson *et al.*, in draft). When AMFm was launched, ADDOs operated in eight regions (Ruvuma, Rukwa, Mtwara, Morogoro, Mbeya, Singida, Pwani, and Lindi), but only dispensers in the TFDA pilot

districts in Ruvuma and Morogoro had previously received training on ACTs (in 2007). In Mtwara and Lindi regions only, a one-day refresher training that included treatment of malaria with ACTs (as well as the use of oral rehydration solutions and family planning) was offered for dispensers with previous nursing training in August 2011. Roll out of ADDOs to additional regions incorporated ACTs into the general training. In September 2012, when the studies presented in this thesis were conducted, ADDO roll out had taken place in six more regions, with an additional six in progress. At this time, RDTs were not permitted in ADDOs. Nationwide ADDO roll out was completed in 2013, with approximately 60% of the 9,000-plus drug shops having completed the training and accreditation process [25].

3.2 Mtwara region

The research presented in this thesis was conducted in Mtwara region in southeastern Tanzania. Mtwara is a primarily rural region located on the southeastern coast with Mozambique on its southern border. The distance from Dar es Salaam to the main urban centre in Mtwara is 558 km [26] on mostly paved road, though in 2012 some unpaved sections proved difficult during the rainy seasons. There is also an airport in Mtwara, with a daily direct flight from Dar es Salaam. Mtwara is composed of six districts (Mtwara Urban, Mtwara Rural, Masasi, Nanyumbu, Newala, and Tandahimba). The main town is in Mtwara Urban, and peri-urban centres are located in Masasi, Newala, and Tandahimba. The road from Mtwara town to Masasi (200 km) is paved, but the majority of roads in the region are not.

The population of Mtwara is 1,270,854, with a density of approximately 76 persons per square kilometre [26]. More than 80% of the population are small-scale farmers [1], and over one third of the population is in the lowest national wealth quintile [4]. The population is mostly Muslim, and adult literacy is 71%, slightly lower than the national average (78%). Mobile phone ownership in the Southern zone (Mtwara and Lindi) is 34% among women and 47% among men. The most common source of mass media is the radio, with 62% of women and 80% of men listening to the radio at least once per week,

and less than 25% of men and 15% of women exposed to TV or newspapers [5]. Coverage with national or community-based health insurance is very low (less than 5%), and approximately 60% are able to access a public health facility within an hour or less [27].

Monthly rainfall in Mtwara in 2012 was highest January – May (180 mm in January, reducing to 55 mm in May), with little rainfall from June to November (range 6 – 15 mm), and increasing again to 44 mm in December [26]. Prevalence of malaria was 15% by reference blood smears among patients seeking care for fever at ADDOs in March 2012 [28], 32% by reference blood smears among patients seeking care for fever in health facilities in July 2012 [13], and 17% by RDT in a household survey in August – September 2012 [27].

There are approximately 150 public health facilities in Mtwara, the majority of which are small dispensaries. There are also approximately 150 ADDOs (subject to turnover) and four pharmaceutical wholesalers located in the region, two each in Mtwara and Masasi towns. By 2011, all drug shops in Mtwara were officially required to have upgraded to ADDO status, but in practice some shops had not yet paid fees or received training but were tolerated as "prospective ADDOs."

Figure 3: Mtwara ADDOs

Prior to AMFm, ACTs were rarely sold in ADDOs in Mtwara. From February 2011 to January 2012, a study in Mtwara and Rukwa regions reported that the availability of AMFm-subsidised ACTs in ADDOs increased from 25% to 88% in Mtwara and from 3% to 62% in Rukwa [29]. The mean retail price of an adult ACT treatment decreased during this time from $1.03 to $0.81, with a median in 2012 of the recommended retail price ($0.64). AL was the primary ACT available, with only a few shops stocking artesunate-amodiaquine. Unlike the previous CHAI pilot in Shinyanga and Dodoma regions [22, 23], degree of remoteness within Mtwara did not have a significant effect on availability of ACTs, although availability in Mtwara remained higher than in the more remote Rukwa region. Shops with a higher number of ADDOs within three kilometres, a higher number of customers, and a higher fraction of customers seeking care for malaria were more likely to stock ACTs [30]. In a related household survey in Mtwara and Rukwa, ACT use among suspected malaria cases increased from 51% in March 2011 to 62% in March 2012, with the largest increase among retail sector patients (31% go 61%) [31].

3.3 The IMPACT2 Project

This research was conducted within the framework of the IMPACT2 project in Tanzania. IMPACT2 is a collaboration of the London School of Hygiene and Tropical Medicine (LSHTM), the U.S. Centers for Disease Control and Prevention (CDC), and Ifakara Health Institute (IHI), with funding from the Bill and Melinda Gates Foundation through the ACT Consortium. The project, which began in 2009, focused on monitoring interventions to improve ACT access and targeting, with the aim of evaluating the national roll out of RDTs and the introduction of AMFm-subsidised drugs in terms of the impact on coverage, equity and quality of malaria treatment. IMPACT2 activities included household surveys, health facility surveys, and qualitative data collection in three regions of Tanzania (Mwanza, Mbeya, and Mtwara) in 2010 and 2012, as well as a 2012 survey of parasitaemia and ACT purchasing among ADDO patients in Mtwara and Mwanza [13, 14, 28]. The project also conducted national drug outlet surveys in

2010 and 2011 as part of the Independent Evaluation of AMFm [32-34]. All other IMPACT2 field work had been completed when data collection for this thesis began.

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4 Research objectives and methods

This chapter outlines the main objective of each of the three research papers presented in this thesis and explains how the research papers in Chapters 5-7 fit together. While most of the methods used are presented in detail in each paper, an overview of the methods is provided, with additional details available in appendices.

4.1 Research objectives

The specific objectives of the research presented in this thesis are:

1. To determine differences in patient characteristics and levels of adherence between patients obtaining AL in public health facilities and ADDOs, and to examine factors associated with adherence in both of these settings (Chapter 6).
2. To evaluate the effect on dispenser knowledge and patient adherence of text message reminders targeted at ADDO dispensers concerning advice to provide when dispensing AL (Chapter 5).
3. To compare the validity of assessing patient adherence with self-reported data compared to smart blister packs (Chapter 7).

In this thesis, the second research objective is addressed first (Chapter 5), with Chapter 6 addressing the first research objective. This order was necessary, as the research paper on the text message intervention in ADDOs was published first, and the subsequent research papers reference its description of methods.

4.2 Overview of study design

The research was composed of three related studies, a cluster-randomised trial (CRT) of a text message intervention, an observational study in public health facilities, and a comparison of methods to

assess adherence. The first two studies relied on adherence measured by self-report and pill count, but in order to assess the validity of this approach, a third study using smart blister packs—a customised electronic monitoring device—was nested within the other two studies.

A CRT was chosen to evaluate the text message intervention. In CRTs, as in other randomised controlled trials, the random allocation of the intervention ensures (theoretically) that known and unknown factors that might affect the outcome are evenly distributed, allowing differences in outcome between control and intervention arms to be attributed to the intervention. In order to minimise contamination between dispensers working in the same or nearby shops, the intervention was delivered at the cluster (ADDO) level. The observational study in public health facilities was conducted in order to address whether or not adherence to AL obtained in ADDOs was lower than in public health facilities. These studies were conducted in parallel, with teams simultaneously working at ADDOs and public health facilities in each district of Mtwara.

Mtwara region was selected as the research site, as this was one of three focus regions for the IMPACT2 umbrella project, along with Mwanza and Mbeya. Mtwara was selected for this adherence study for several reasons. Both Mtwara and Mbeya had established ADDOs, but Mwanza did not, and DLDB could not officially supply ACTs. In Mbeya, the low prevalence of malaria might have resulted in slow patient enrolment compared to Mtwara region, where transmission is moderately high. Finally, an IHI office is located in Mtwara and could help with field logistics.

ADDO census. Preliminary data collection for the CRT began in May 2012 with a census and brief survey of all ADDOs in Mtwara. The primary purpose of the census was to build a sampling frame for the CRT and collect data to guide the sampling process in order to minimise contamination between control and intervention ADDOs. Selection and randomisation of ADDOs, as well as selection of public health facilities for the observational study, are described further in Chapters 5 and 6.

Text message intervention. The text message intervention is described in Chapter 5. Briefly, dispensers at selected ADDOs were visited prior to beginning the intervention to invite participation. Messages were scheduled in advance and sent automatically Monday – Friday of the first four weeks, and Monday, Wednesday, Friday of the next 10 weeks. Content of text messages was based on ACT dispensing instructions. Each of the seven content messages was paired with a unique quote to encourage reading or a question based on the content of a previous message. Respondents that replied correctly (at their own expense) were compensated with extra airtime.

Enrolment of outlets. From September – November 2012, both control and intervention ADDOs and selected public health facilities were visited and asked to participate in the research. Dispensers were provided with smart blister packs of AL (discussed in Chapter 7) and asked to register all patients that obtained any drug for fever or malaria at the outlet on a study form (Appendix 1a-b). The intention was to register 12 patients obtaining ACTs in one week per outlet, but it took 2-3 weeks to recruit this number in some outlets.

Patient and dispenser interviews. Registered patients obtaining AL were visited at home on day 4 for a structured interview covering when and how each dose of AL was taken (Appendix 1c) and collection of blood samples and blister packs. Determination of patient adherence is described in Chapters 5-7. Interviews of ADDO dispensers were conducted from mid-October – November 2012, following completion of patient interviews in a given district. Dispensers were asked about their knowledge of advice to provide patients when dispensing AL using open-ended questions. Responses were recorded verbatim and evaluated against a pre-specified description of correct responses.

Key informant interviews (KIIs). Key informant interviews were conducted in each district with the DMO and, when available, the District Pharmacist, the District Nursing Officer, and / or the Malaria Focal Person. Data were collected on ADDO roll out, training, supervision, inspection, and community sensitization, as well as availability of ACTs and RDTs in health facilities, and other malaria control and

research activities. The data are not presented separately in this thesis but inform the interpretation of the studies described in the research papers.

Socioeconomic indices. To determine socioeconomic status, data were collected from patients on ownership of household possessions, housing characteristics, and access to utilities, based on standard Demographic and Health Survey variables (http://www.measuredhs.com). Socioeconomic indices were calculated using principal component analysis, with the factor scores from the first principal component used as weights [1]. Scores were divided into quintiles, and the proportions of patients in each quintile were presented in tables.

Registration of CRT and ethical approvals. The CRT was registered with Current Controlled Trials, ISRCTN83765567. Both the CRT and the observational study were submitted together for ethical approval to LSHTM and IHI. An amendment was also submitted to LSHTM when it was decided to test patients with RDTs at the interview, in addition to collecting blood smears and filter papers (this amendment was included in the original protocol submitted to IHI). Approval letters are included in Appendix 2.

When enrolling outlets to participate in the study, a consent form with a standard introduction to the research was read and signed by a dispenser at each outlet (Appendix 1a). Informed consent was also collected from patients and dispensers prior to interview.

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5 Text message intervention in ADDOs

5.1 Introduction

This chapter covers the first of three research papers presenting results of the studies conducted for this thesis. Published online in the *American Journal of Hygiene and Tropical Medicine* in July 2014, this paper addresses the second research objective, evaluating the effect on dispenser knowledge and patient adherence of text message reminders targeted at ADDO dispensers concerning advice to provide when dispensing AL. This chapter is placed before the chapter addressing the first research objective (Chapter 6), as this research paper was published first, and the second and third papers (Chapters 6-7) refer to methods presented in this paper.

Details of the ADDO census, selection, and randomisation, as well as the full schedule of text messages are included in Appendix 3.

5.2 Research paper (cover sheet on next page)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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Principal Supervisor	David Schellenberg
Thesis Title	Evaluating patient adherence to aretemether-lumefantrine obtained from public and private drug outlets in Tanzania

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Cluster Randomized Trial of Text Message Reminders to Retail Staff in Tanzanian Drug Shops Dispensing Artemether-Lumefantrine: Effect on Dispenser Knowledge and Patient Adherence

Katia Bruxvoort,* Charles Festo, Admirabilis Kalolella, Matthew Cairns, Peter Lyaruu, Mitya Kenani, S. Patrick Kachur, Catherine Goodman, and David Schellenberg

Department of Global Health and Development, Department of Infectious Disease Epidemiology, and Department of Disease Control, London School of Hygiene and Tropical Medicine, London, United Kingdom; Impact Evaluation Thematic Group, Ifakara Health Institute, Dar es Salaam, Tanzania; Malaria Branch, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract. Artemisinin combination therapies are available in private outlets, but patient adherence might be compromised by poor advice from dispensers. In this cluster randomized trial in drug shops in Tanzania, 42 of 82 selected shops were randomized to receive text message reminders about what advice to provide when dispensing artemether-lumefantrine (AL). Eligible patients purchasing AL at shops in both arms were followed up at home and questioned about each dose taken. Dispensers were interviewed regarding knowledge of AL dispensing practices and receipt of the malaria-related text messages. We interviewed 904 patients and 110 dispensers from 77 shops. Although there was some improvement in dispenser knowledge, there was no difference between arms in adherence measured as completion of all doses (intervention 68.3%, control 69.8%, p [adjusted] = 0.6), or as completion of each dose at the correct time (intervention 33.1%, control 32.6%, p [adjusted] = 0.9). Further studies on the potential of text messages to improve adherence are needed.

INTRODUCTION

Patient adherence to treatment is an important step in ensuring the effectiveness of artemisinin-based combination therapies (ACTs) for malaria.[1] Incomplete adherence to recommended treatment can result in poor clinical outcomes, undermine the effectiveness of case management as a tool for malaria control, and may contribute to the selection of drug-resistant malaria parasites.[2,3] ACTs are first-line treatment of *Plasmodium falciparum* malaria in the public sector of most malaria-endemic countries, with patient adherence reported to range widely from 39% to 100%.[4,5] Many patients seek care for malaria in the private retail sector.[6–9] The proportion of private sector clients obtaining ACTs has increased over time as ACTs have become more widely known, and their price has fallen, particularly in settings where they have been subsidized by programs such as the Affordable Medicines Facility-malaria (AMFm).[10]

Although access to effective antimalarials in the private sector may have increased, drug sellers may not always provide patients with appropriate doses or advice, raising concerns about patient adherence, though evidence is very limited. Only five studies have specifically assessed patient adherence to antimalarials obtained in the private retail sector.[11–15] Of these, ACTs were used only in one study by Cohen and others (2012)[11] in Uganda, which reported 66% of patients seeking care from drug shops were adherent. As ACTs become more available in the private sector, it becomes increasingly important to understand patient adherence and the effects of interventions intended to improve adherence. Supporting interventions, such as shopkeeper training, have previously succeeded in increasing the proportion of patients who receive and complete the recommended dose of non-ACT antimalarials,[13,16] but such interventions have yet to be tested on a national scale or applied to ACTs.

Mobile phones are a promising tool for the delivery of healthcare interventions as coverage of mobile networks and handset ownership increases.[17–19] Text messaging, the least expensive mobile phone function, has been used in malaria control settings for commodity monitoring, disease surveillance, and pharmacovigilance.[20] In addition, a trial in public health facilities in Kenya[21] showed that 6 months of text message reminders improved public health workers' management of pediatric malaria by 24% points immediately after the intervention, and the improvements were sustained for at least 6 months after the intervention was withdrawn. The text message reminders were well accepted by health workers,[22] inexpensive, and cost-effective.[23]

Given the concerns over inadequate patient adherence to ACTs delivered through the private retail sector, and the potential benefit of text-message interventions to enhance adherence, we designed and completed a cluster randomized trial in southern Tanzania to assess the effect of text message reminders to drug shop workers on patient adherence to artemether-lumefantrine (AL). We also evaluated the effect of text messages on dispenser knowledge and advice.

The private retail sector in Tanzania is an important source of treatment of malaria,[24,25] and ACT availability in such outlets increased after the implementation of AMFm in 2010. Another key intervention in Tanzania's private sector has been the creation of accredited drug dispensing outlets (ADDOs) by the Tanzania Food and Drug Administration (TFDA) to improve regulation of drug shops and quality of medicines. ADDOs are drug shops that have been upgraded through a process of training and certification and are allowed to sell a limited number of prescription-only drugs, including some antibiotics and ACTs.[26,27]

METHODS

Study setting. The study was conducted in Mtwara, a rural region in southeastern Tanzania with 35.5% of the population in the lowest national wealth quintile.[28] Prevalence of malaria

*Address correspondence to Katia Bruxvoort, 15-17 Tavistock Place, London, WC1H 9SH. E-mail: katia.bruxvoort@lshtm.ac.uk

among children 6–59 months of age in Mtwara was 17.4% in the 2011–2012 HIV/AIDS and Malaria Indicator Survey[29] and 23% in a survey of patients seeking treatment at private drug shops.[30] AL has been recommended as the first-line treatment of malaria since 2004, although it was not available in public health facilities until 2006. The recommended treatment regimen is six doses of AL over 3 days, with 1–4 tablets (20 mg artemether/120 mg lumefantrine) per dose depending on the weight/age band. National guidelines state that the second dose should be taken 8 hours after the first dose, followed by the remaining doses morning and evening of the second and third days.[31]

In Mtwara, ADDO accreditation commenced in 2006, and officially only accredited drug stores are allowed to function. In reality, a large number of non-accredited shops exist because of a lack of training, unpaid fees, or administrative delays. These shops are tolerated by regulating authorities and considered "prospective ADDOs." Before AMFm, ACTs were not commonly available in ADDOs in Mtwara, and dispenser training on ACTs was limited, but ACT availability significantly increased after AMFm implementation, with 88% of ADDOs stocking ACTs in Mtwara in August 2011.[32] To support AMFm roll out, TFDA offered a 1 day refresher training that included treatment of malaria with ACTs to dispensers with previous nursing training in Mtwara in August 2011.

Sample size calculations. We based the sample size for this two arm cluster randomized trial on data from the public sector in Tanzania, where patient adherence to AL was 65–98%(Khatib R, unpublished data).[33–35] We assumed lower adherence to AL obtained at ADDOs in Mtwara (60%) and powered the study to detect a 15% point increase in the intervention arm. We wanted to recruit a small number of patients per cluster to reduce the potential bias caused by increasing community awareness of the study's objectives. Assuming a coefficient of variation of 0.25, 80% power, 5% significance, and 20% loss to follow-up, 13 patients from 36 outlets in each arm were required, a total of 468 patients per arm.

Selection of study ADDOs. In May 2012, we conducted a census of all drug shops in Mtwara (ADDOs or prospective ADDOs). Data were collected on the characteristics of owners and dispensers, ACT stocks and sales, and global positioning system (GPS) coordinates. ADDOs were excluded from the sampling frame if they had sold fewer than five antimalarial treatments in the previous week, no dispensers used a mobile phone, the shop was located on the border with Mozambique or was not accessible, or the owner refused to participate (Figure 1). The final sampling frame consisted of 131 ADDOs. The 82 ADDOs were selected sequentially at random, with any ADDOs within 400 m of a selected ADDO, or any ADDOs where staff from a selected ADDO also worked, removed from the sampling frame. The selected ADDOs were then stratified by location in urban or rural wards, and the intervention was randomly allocated to 29 of 57 urban ADDOs and 13 of 25 rural ADDOs.

Intervention design. We designed seven content messages about advice that dispensers should provide when dispensing AL (Figure 2). The messages were derived from the government refresher training booklet and reflected the recommended practices for dispensing AL. Messages were pilot tested in ~20 ADDOs in a semi-urban district outside of Dar es Salaam. Dispensers at these ADDOs were sent each potential message in turn and asked to explain their understanding of the meaning and relevance of each message. Dispensers were also asked if they would find receipt of the messages helpful, how often they would like to read the messages, and whether complementary components such as quotes or questions would encourage reading. Phrasing and frequency of the messages were adjusted based on feedback received during the pilot.

Before sending the first message, the 42 ADDOs in Mtwara randomized to the intervention arm were visited to invite participation and collect an updated list of mobile numbers for all dispensers. Messages began in July 2012 and were sent in random order once per day Monday–Friday for the first 4 weeks, followed by once per day Monday, Wednesday, and Friday for the next 10 weeks. Messages were written in Swahili and scheduled in advance on an automated platform, with each message paired with a different complementary component each time to promote interest. Complementary components consisted of inspirational quotes or proverbs or, once per week, a quiz question on message content that earned correct respondents free air time (500 TSH or $.30). Over the 14-week period, 49 messages were sent to each of 60 dispensers, and detailed delivery reports were kept for each message.

Data collection. From September through November 2012, dispensers at ADDOs in the intervention and control arms were visited by study supervisors and given a standard introduction about study objectives. To limit patients' awareness of our primary interest in adherence, which could have led to a biased assessment, dispensers were told we were studying how patients chose to treat fever and would visit some, but not all, patients at their homes. They were asked to fill out a registration form for all patients purchasing any treatment of fever, including the day and time of their ADDO visits, the patients' names, the drugs purchased, and a description of where the patients lived. Dispensers were provided with blister packs of AL that they could then sell to patients needing treatment of malaria. Study staff visited ADDOs every day to check and collect registration forms for 1–3 weeks, or until 12–15 patients purchasing AL were registered if quicker.

Eligible patients who obtained AL were identified from the registration forms and assigned patient identification numbers (recorded on follow-up forms). Patients were followed up ~68–72 hours after their ADDO visit, according to a predefined schedule, and all attempts to locate and interview patients were recorded. Where written informed consent was given, patients or their caregivers were asked about demographic and socioeconomic characteristics, treatment-seeking history, illness symptoms, detailed information about each dose of AL taken and the advice provided by the ADDO dispenser. Blister packs were requested for a pill count, and blood samples were collected for a blood smear and a malaria rapid diagnostic test (mRDT) (Pf-specific from ICT Diagnostics, Cape Town, South Africa). Blood smears were stained in the field and transported to the Ifakara Health Institute, where they were double-read by two microscopists blinded to results from each other and the mRDT, with discrepant results read by a third microscopist.

Adherence was defined in two ways.[5] Patients were considered to have "verified completed treatment" if they reported taking all doses by the time of the follow-up visit and a pill count verified that no pills remained in the blister pack, if available. The second, more stringent definition included

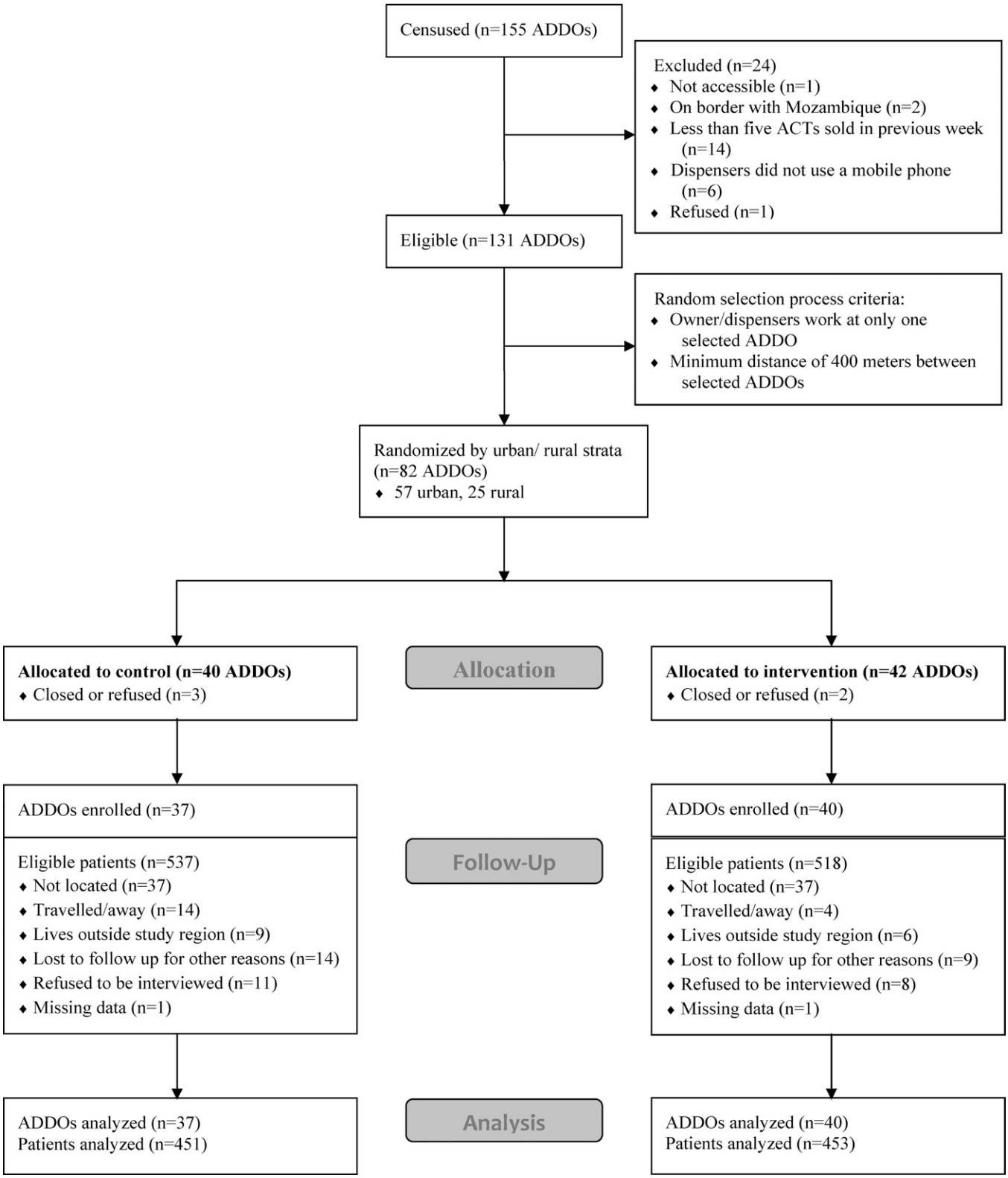


FIGURE 1. Consort-like style flow diagram of trial.

a time component, based on patient reports of the time each dose was taken using the Swahili times of day: "alfajiri" (early morning), "asubuhi" (morning), "mchana" (afternoon), "jioni" (evening), "usiku" (night), and "usiku sana" (late night). Patients were considered to have "verified timely completion" if they took the second dose at the Swahili time of day corresponding with 8 hours after the first dose, and then took each of the remaining doses at the Swahili time of day

1. Make sure the **first dose** of AL is taken under the **observation** of the dispenser.
2. Advise the patient to take the **second** dose of AL exactly **8 hours** after the first dose then take the remaining doses every 12 hours for two more days.
3. Explain to the patient that AL should be taken with **fatty foods.**
4. Tell the patient that if he/she **vomits** within a half hour of taking a dose, he/she must return to get a **replacement dose.**
5. Advise the patient to finish all tablets within **three days** as this will kill all the parasites.
6. Advise the patient to **finish** the treatment even if he/she feels **better** so as to kill all the malaria parasites.
7. Tell the patient that very **minor side effects** can occur, but they should **continue** taking the treatment.

FIGURE 2. Content of text messages sent to dispensers in the intervention arm.

corresponding with 12 hours after the previous dose, verified by the absence of pills in the blister pack. For ease of reading, we hereafter refer to these definitions as "completed treatment" and "timely completion."

After completion of patient interviews, dispensers working at the study ADDOs were interviewed on ADDO characteristics, demographics, receipt of study text messages, and advice they would give to patients when dispensing AL. To assess knowledge corresponding with message content, we used an open-ended question, e.g., "I would like to ask about which advice you think you should provide to a person of any age taking treatment for malaria. For the following topics (e.g., "when to take the second dose" or "what to do with the pills if the patient feels better," etc.) tell me if advice on this topic is important or not, and if so, what advice you would provide." Responses were recorded verbatim and evaluated by the study leader using predetermined criteria based on message content.

Data entry and analysis. All patient and dispenser interview data were collected using personal digital assistants, and data extracted from study forms (census, registration, and follow-up forms) were double entered into Microsoft Access databases (Microsoft Corp., Redmond, WA). Data were analyzed in Stata 11.0 (Stata Corporation, College Station, TX). Primary outcomes were analyzed by intention-to-treat. Comparison of adherence was based on a *t* test of the proportion adherent in each cluster. A list of potentially important confounders was identified a priori consisting of ADDO accreditation certificate, number of customers purchasing ACTs in the previous week, dispenser medical qualification, dispenser training on ACTs, patient age, and patient education. Adjustment for variables on this list found to be unbalanced between arms was performed by fitting a logistic regression model to the individual data and performing analysis on the aggregated residuals, as described by Bennett and colleagues.[37]

Ethics. All questionnaires, consent forms, and other study documents were translated into Swahili and piloted before use. Written informed consent was collected from dispensers before census, patient registration and interview, and from patients or their caregivers prior to interview. The study protocol was approved by the ethical review boards of Ifakara Health Institute and London School of Hygiene and Tropical Medicine. The Centers for Disease Control and Prevention (CDC) investigators provided technical assistance in design and analysis but were not engaged in data collection. The trial is registered with Current Controlled Trials, ISRCTN83765567.

RESULTS

Figure 1 shows the trial profile. Of the 82 randomized ADDOs, 37 from the control arm and 40 from the intervention arm participated in the study. The number of registered patients eligible for follow-up was 537 in the control arm and 518 in the intervention arm, with ~15% of patients in each arm lost to follow-up. Most outlets were in urban wards (70% in both arms), had a single dispenser, and had at least some ACTs in stock on the day of interview (Table 1). Of 51 dispensers in the control arm and 59 in the intervention arm, ~80% in both arms were female and had a low-level medical qualification, mostly nurse assistants (Table 2). Though low in both arms, more ADDOs in the control arm compared with the intervention arm were able to show an accreditation certificate (43% versus 20%, respectively). However, the difference in the percentages of dispensers that had received training on ACTs was not as pronounced (69% in the control

TABLE 1
Characteristics of accredited drug dispensing outlets (ADDOs)

	Control	Intervention
Number (*N*)	37	40
Number urban (%)	26 (70%)	28 (70%)
Median number of dispensers per ADDO (range)	1 (1–3)	1 (1–4)
Number with one or more trained medical staff (%)*	36 (97%)	37 (92%)
Number with any ACTs in stock on day of interview (%)	35 (95%)	40 (100%)
Number with all four weight-based packs in stock on day of interview (%)	11 (30%)	14 (35%)
Median number of customers purchasing ACTs in last 7 days (range)	13 (0–82)	19 (0–147)
Number with ADDO accreditation certificate (%)	16 (43%)	8 (20%)
Number with drinking water available in ADDO (%)	30 (81%)	37 (93%)

*Medical staff is defined as pharmacists, pharmacist assistants, medical doctors, assistant medical doctors, clinical officers, assistant clinical officers, midwives, nurses, nurse assistants, and laboratory technologists. Most were nurse assistants or nurses.
ACTs = artemisinin-based combination therapies.

TABLE 2
Characteristics of dispensers (post-intervention)

	Control	Intervention
Total number of dispensers	53	59
Number interviewed (*N*)	51	59
Male (%)*	10 (20%)	13 (22%)
Age (%)*		
Under 35 years of age	18 (35%)	23 (39%)
35–49 years of age	23 (45%)	17 (29%)
50 years and above	10 (20%)	19 (32%)
Number with a medical qualification (%)*†	44 (86%)	47 (81%)
Socioeconomic status (%)‡§		
1st quintile (most poor)	9 (18%)	13 (22%)
2nd quintile	12 (24%)	10 (17%)
3rd quintile	9 (18%)	13 (22%)
4th quintile	8 (16%)	14 (24%)
5th quintile (least poor)	12 (24%)	9 (15%)
Number that had attended training on ACTs (%)*	35 (69%)	35 (60%)
Median year of training (range)	2011 (2005–2012)	2009 (2001–2012)

*Data missing for one dispenser in intervention arm.
†Medical staff is defined as pharmacists, pharmacist assistants, medical doctors, assistant medical doctors, clinical officers, assistant clinical officers, midwives, nurses, nurse assistants, and laboratory technologists. Most were nurse assistants or nurses.
‡Data missing for one dispenser in control arm.
§Wealth quintiles determined using a principal component analysis of sampled dispensers based on standard Demographic and Health Survey variables.

arm versus 60% in the intervention arm), though the median year of training was more recent in the control arm (2011 versus 2009).

Characteristics of patients were well balanced between arms (Table 3). A high percentage of patients (36% in the control arm and 38% in the intervention arm) had sought care before attending the study ADDO, with most patients going to a kiosk or general shop and only 7% of patients in the control arm and 4% in the intervention arm going to a public health facility. Approximately 90% reported symptoms of fever or headache, and approximately half had upset stomachs or nausea. Based on an mRDT taken at the time of follow-up, 28% in the control arm and 25% in the intervention arm tested positive, with only 1.4% and 1.6%, respectively, testing positive by study blood smear. (Some degree of discrepancy is expected because of the persistence of HRP2 detected by the mRDT.)

Seventy percent of dispensers received at least 75% of the text messages. The median percentage of messages received was 86%, with 20% of dispensers receiving no messages (Figure 3). Table 4 presents results of the dispenser interviews on knowledge of advice to provide patients when dispensing AL. Dispensers in the intervention arm reported slightly better knowledge of the correct AL regimen for adults in the intervention arm compared with the control arm (90% versus 78%; adjusted prevalence ratio [aPR] = 1.2 (95% confidence interval [CI]: 0.95, 1.5); p [adjusted] = 0.0748), though knowledge of the correct regimen for a child aged four weighing 20 kg was lower than for adults in both arms (75% versus 64%; aPR = 1.2 [0.85, 1.7]; p [adjusted] = 0.2). Dispenser knowledge was considerably higher in the intervention arm than the control arm on advice to take AL with fatty food (60% versus 20%; aPR = 3.4 [95% CI: 1.6, 7.1]; p [adjusted] < 0.0001) and to continue to take AL if minor side effects occur (68% versus 43%; aPR = 1.6 [95% CI: 1.0, 2.4]; p [adjusted] = 0.0188). However, surprisingly high dispenser knowledge (87–99%) was recorded in both arms on advice to complete treatment even if feeling better, advice to return to the ADDO or go to a health facility if the condition worsens, and advice to take the second dose after 8 hours (Table 4). Knowledge on advising patients to take a replacement dose in case of vomiting within half an hour of taking a dose was lower (55% versus 50%), with no difference observed between arms.

Table 5 shows that ~60% of patients in both arms reported being told how to take AL correctly, with similar percentages reporting being told to take the second dose after 8 hours and to complete treatment even if feeling better, indicating that dispensers were providing some advice even in the absence of the intervention. However, no differences were found between control and intervention arms for any piece of advice. Less than 5% of patients in both arms reported being told about vomiting, side effects, or taking AL with fatty food, and < 10% in both arms took the first dose of AL at the ADDO.

There was no difference in patient adherence between arms (Table 6). Completed treatment was 70% in the control arm and 68% in the intervention arm (adjusted risk ratio

TABLE 3
Characteristics of patients

	Control	Intervention
Number (*N*)	451	453
Male	240 (53%)	211 (47%)
Age*		
Under 3 years	81 (18%)	78 (17%)
3 years to under 8 years	104 (23%)	91 (20%)
8 years to under 12 years	41 (9%)	42 (9%)
12 years and above	225 (50%)	242 (53%)
Blister pack obtained		
1 × 6 (6 tablets)	109 (24%)	107 (23%)
2 × 6 (12 tablets)	95 (21%)	88 (19%)
3 × 6 (18 tablets)	50 (11%)	43 (10%)
4 × 6 (24 tablets)	197 (44%)	215 (48%)
Patient (or caregiver if patient below age 12) completed primary school†	323 (72%)	343 (76%)
Socioeconomic status‡		
1st quintile (most poor)	87 (19%)	94 (21%)
2nd quintile	99 (22%)	82 (18%)
3rd quintile	97 (22%)	84 (19%)
4th quintile	85 (19%)	96 (21%)
5th quintile (least poor)	83 (18%)	97 (21%)
Slept under any bed net the night before the follow up interview	321 (71%)	357 (79%)
Sought care before attending study ADDO	171 (38%)	163 (36%)
Median days since illness onset before seeking care at ADDO§	1	1
Symptoms¶		
Fever or headache	410 (91%)	416 (92%)
Respiratory	34 (8%)	34 (8%)
Stomach upset	220 (49%)	209 (46%)
Other‖	216 (48%)	211 (47%)
mRDT positive at follow up**	121 (28%)	108 (25%)
Blood smear positive at follow up††	6 (1.4%)	7 (1.6%)

*Age categories based on recommended age breakdown for artemether-lumefantrine (AL) blister packs in Tanzania.
†Caregiver education missing for 3 patients < 12 in intervention arm.
‡Wealth quintiles determined using a principal component analysis of sampled patients based on standard Demographic and Health Survey variables.
§Eleven patients in control arm and 4 patients in intervention arm did not remember the number of days after illness onset when they sought care at the study accredited drug dispensing outlets (ADDO).
¶Percents do not add to 100% as patients experienced multiple symptoms.
‖Includes fatigue, body aches, dizziness, shaking, convulsions, unusually-colored urine, yellow mouth/eyes/body, etc.
**Malaria rapid diagnostic test (mRDT) data missing for 12 patients in control arm and 12 patients in intervention arm.
††Blood smear data missing for 18 patients in control arm and 13 patients in intervention arm.

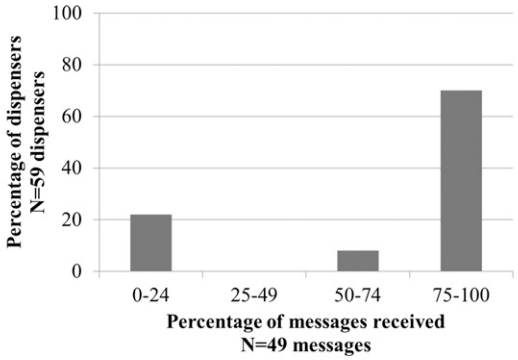


FIGURE 3. Percentage of text messages received by dispensers in the intervention arm.

[aRR] = 0.96 [95% CI: 0.82, 1.1]; *p* [adjusted] = 0.6), with a similar percentage of patients adherent to each of the four age-appropriate blister packs and no important differences between arms. The mean number of doses taken by non-adherent patients was four in both arms, and the most common reported reasons for non-adherence included planning to take the medication later, forgetting to take the tablets, feeling better, and other reasons (Figure 4). Timely completion was much lower, with 33% of patients in both arms taking all doses at appropriate times. A per protocol analysis, excluding patients attending ADDOs where at least one dispenser did not receive any messages, had no impact on results.

DISCUSSION

We have reported results from a cluster randomized trial of a text message intervention directed at drug shop dispensers to improve patient adherence to ACTs in Tanzania. The intervention increased dispenser knowledge of some components of advice to provide patients when dispensing AL, but knowledge of other components was already very high in the absence of the intervention. The improvements in knowledge did not translate into an increase in information patients reported receiving, even though patients commonly reported receiving some advice. There was no difference in adherence of patients to the ACT regimen between the arms.

Adherence by completed treatment was < 70% to ACTs obtained from ADDOs, comparable to the 66% adherent by the same definition in the study by Cohen and others (2012)[11] in the private retail sector in Uganda. However, timely completion was only 33% in our study, indicating that even patients who complete treatment may do so with poor adherence to the recommended schedule. Both of these results are comparable to reported adherence to ACTs obtained from public health facilities, where studies under real life conditions have found adherence of 64–77% for completed treatment verified by pill count and 39–75% for timely completion verified by pill count,[5] including one study from Tanzania.[35] Two other studies from public health facilities in mainland Tanzania using different definitions and methods have reported higher adherence (88.3% and 90%).[33,34]

Although the text message intervention targeting dispensers was not effective at improving patient adherence, there was a marked increase in dispenser knowledge of advising patients to take AL with fatty foods or milk and to continue AL even if minor side effects occurred. However, knowledge in both arms was surprisingly high, particularly on advising patients to take the second dose after 8 hours, to complete treatment even if feeling better, and to seek further care if the condition worsens. This could reflect the recent ADDO trainings in Mtwara, raising the possibility that the intervention's impact could have been different in the absence of recent training.

Knowledge did not necessarily result in the provision of advice, even though some advice was provided. For example, 98% of dispensers in both arms knew it was important to advise patients to complete treatment even if feeling better, but only 60% of patients reported receiving this advice. Other advice was much less commonly provided, with < 5% of patients in both arms reporting being advised on what to do in case of minor side-effects or vomiting, even though dispenser knowledge of this advice was much higher. This may be because the dispensers did not deem the advice helpful to their business or to the patients, as it could heighten a negative perception about the effects of their products. Dispensers may have also perceived that clients were in a hurry or not receptive to advice. Alternatively, patients or caretakers may not have recalled the advice given to them several days before. Exit interviews or mystery shopper surveys may have been useful in assessing whether advice was communicated, but these methods also have limitations, such as greater potential for a Hawthorne effect and ethical challenges.

TABLE 4
Dispenser knowledge of correct advice (mean of cluster summaries)

	Control* (*N* = 37) % (SD)	Intervention* (*N* = 40) % (SD)	Adjusted prevalence ratio (95% CI)†	Adjusted *P* value†
Proportion that gave correct advice on:				
Correct AL regimen for adult‡	78.4 (38.3)	90.0 (33.7)	1.19 (0.95, 1.49)	0.075
Correct AL regimen for a child (4 years and 20 kg)‡	63.5 (46.6)	74.6 (40.4)	1.20 (0.85, 1.70)	0.2
Take with fatty food	20.3 (38.1)	60.0 (45.6)	3.41 (1.63, 7.12)	0.0001
Continue treatment if minor side effects occur	42.8 (42.8)	67.5 (45.2)	1.58 (1.03, 2.42)	0.019
Return to ADDO or go to a health facility if condition worsens	91.0 (25.3)	100.0	1.04 (0.84, 1.31)	0.7
Take second dose after 8 hours	86.9 (32.2)	97.5 (15.8)	1.11 (0.93, 1.32)	0.1
Take replacement dose in case of vomiting within half hour of taking dose	49.5 (45.7)	55.0 (46.4)	1.20 (0.77, 1.86)	0.4
Complete treatment even if feeling better	98.6 (8.2)	98.8 (7.9)	1.07 (0.88, 1.30)	0.5

*Total number of dispensers interviewed was 51 in the control arm and 59 in the intervention arm.
†Adjusted for accredited drug dispensing outlet (ADDO) accreditation, number of customers at ADDO purchasing artemisinin-based combination therapies (ACTs) (< 20 vs. 20 or more), dispenser medical qualification, and training on ACTs
‡To be considered correct, responses had to identify artemether-lumefantrine (AL) as first-line treatment and specify that six doses should be taken, with each dose consisting of four pills (adult) or 2 pills (child 4 years of age). Dose intervals considered correct included (A) taking a dose morning and evening for 3 days or (B) taking the second dose 8 hours after the first dose and the remaining doses 12 hours apart (or morning and evening for the next 2 days).

TABLE 5
Patient report of advice received from dispenser (mean of cluster summaries)

	Control* ($N = 37$) % (SD)	Intervention* ($N = 40$) % (SD)	Adjusted prevalence ratio (95% CI)†	Adjusted P value†
Explained correct dose regimen‡	60.6 (21.2)	62.9 (21.5)	1.00 (0.84, 1.20)	0.9
Told to take second dose after 8 hours	64.2 (19.6)	63.0 (20.2)	1.00 (0.87, 1.15)	0.9
Told to complete treatment even if feeling better	61.3 (25.3)	59.3 (27.3)	0.94 (0.76, 1.17)	0.5
Told not to give drug to anyone else or save for future illnesses	41.3 (23.3)	35.1 (25.1)	0.88 (0.65, 1.18)	0.4
Told to return to ADDO or go to a health facility if condition worsens	34.1 (20.5)	35.0 (22.4)	1.01 (0.75, 1.35)	0.9
Told to take replacement dose in case of vomiting	3.3 (8.9)	3.2 (3.2)	1.48 (0.56, 3.90)	0.5
Told about possible side effects	2.8 (5.1)	2.0 (5.1)	0.60 (0.13, 2.77)	0.4
Told to take each dose with fatty food or milk§	2.2 (8.4)	4.2 (9.7)	1.70 (0.40, 7.24)	0.4
First dose was observed at ADDO	5.4 (9.1)	6.9 (12.7)	1.32 (0.63, 2.76)	0.5

*Total number of patients interviewed was 451 in the control arm and 453 in the intervention arm.
†Adjusted for accredited drug dispensing outlet (ADDO) accreditation, number of customers at ADDO purchasing artemisinin-based combination therapies (ACTs) (< 20 vs. 20 or more), dispenser medical qualification, and training on ACTs
‡To be considered correct, responses had to include the correct number of pills per dose for blister pack obtained, two doses per day, and 3 days duration (or 4 days to account for artemether-lumefantrine [AL] obtained late on Day 1)
§If taking with any food or milk is considered correct, percentages increase to 60.2 (22.1) in the control arm and 58.8 (26.0) in the intervention arm, $P = 0.8$)

We intentionally avoided telling dispensers that the purpose of our study was to improve patients' adherence. Although dispensers receiving text messages were aware that the content focused on advising patients about the correct use of AL, we did not mention the objective to dispensers in either arm to avoid this information being relayed to patients, who might then change their behavior because they expected their adherence to be monitored.[5] However, if this intervention were to be scaled up outside the study context, one might include greater emphasis on adherence and its value in communications with dispensers, which might in turn increase the likelihood that they would provide appropriate advice.

The evaluation of patient adherence relied on self-reported data from patients or their caregivers, which may be subject to recall and social desirability bias. We inspected blister packs for the 80% of patients who could provide them and identified only 10 patients (1%) that had reported completing all doses but had pills remaining. On the other hand, patients may have removed pills from the packaging to consume at a later time. Even though Swahili times of day, based on sunrise and sunset, were used to assess timely completion, patients or their caregivers may not have remembered when each dose was taken or may have provided the expected responses to avoid being seen as negligent.

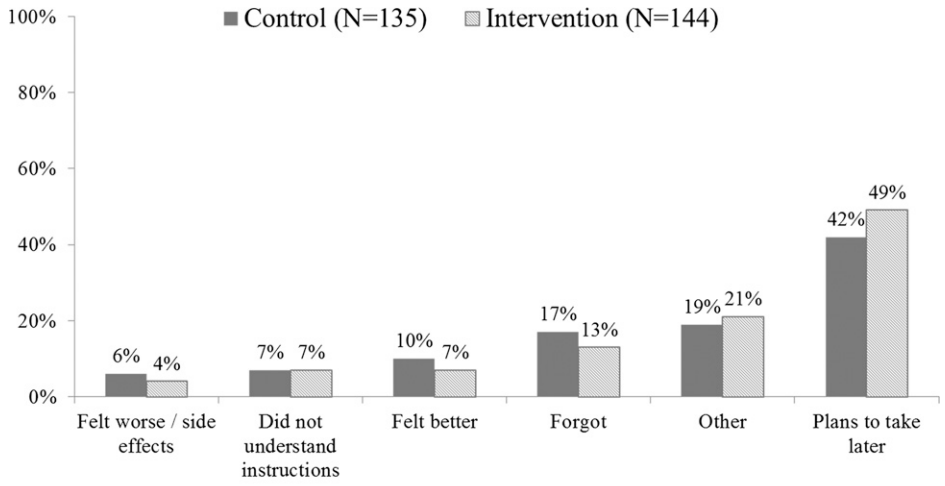
A similar text message intervention targeting health workers in public health facilities in Kenya found significant improvements in health worker case management of pediatric malaria.[21] The primary outcome measure by Zurovac and colleagues included completion of four treatment tasks (e.g., prescribing AL) and at least four of six dispensing and counseling tasks, of which the biggest improvements were seen in giving the first dose at the health facility and advising patients to take the second dose after 8 hours, take each dose after a meal, and what to do in case of vomiting. Although we found strong evidence in the intervention arm of improved dispenser knowledge of advice to take each dose with a fatty meal, we recorded high dispenser knowledge in both arms of advice to take the second dose after 8 hours and no difference between arms in knowledge of advice on what to do in case of vomiting. We also recorded < 10% of patients in either arm taking the first dose of AL at the ADDO, even though drinking water was available at many ADDOs. The contrasts between our findings and those of Zurovac and colleagues could reflect the private drug shop setting, as we found patients' relatives often seek care at ADDOs on behalf of patients, in contrast to public health facilities where patients themselves must be present for a clinical exam. Health workers in public health facilities may also be more accustomed to taking on advisory roles than dispensers in private drug shops and less concerned with making a profit.[37]

Interventions involving training of dispensers in the private retail sector, although limited in number, have improved dispenser knowledge across a range of diseases and settings, but the impact of improved knowledge on dispenser and patient behavior has been mixed.[37,38] Even fewer studies have reported effects of an intervention targeted at retail dispensers

TABLE 6
Patient adherence (mean of cluster summaries)

	Control* ($N = 37$) % (SD)	Intervention* ($N = 40$) % (SD)	Adjusted prevalence ratio (95% CI)†	Adjusted P value†
Completed treatment‡	69.8 (20.9)	68.3 (23.4)	0.96 (0.82, 1.12)	0.6
1 × 6 (6 tablets)	68.2 (33.3)	73.4 (30.9)	1.04 (0.81, 1.33)	0.7
2 × 6 (12 tablets)	62.0 (33.4)	70.7 (40.5)	1.10 (0.85, 1.43)	0.5
3 × 6 (18 tablets)	73.0 (35.7)	62.5 (39.7)	0.86 (0.66, 1.13)	0.4
4 × 6 (24 tablets)	73.8 (23.1)	67.8 (29.1)	0.89 (0.74, 1.08)	0.2
Timely completion§	32.6 (18.4)	33.1 (21.6)	1.01 (0.76, 1.36)	0.9
1 × 6 (6 tablets)	37.2 (36.7)	26.4 (34.5)	0.67 (0.35, 1.28)	0.2
2 × 6 (12 tablets)	25.7 (24.9)	33.1 (36.6)	1.32 (0.86, 2.00)	0.4
3 × 6 (18 tablets)	35.5 (41.3)	37.9 (41.4)	1.02 (0.57, 1.81)	0.9
4 × 6 (24 tablets)	38.1 (27.6)	34.8 (29.3)	0.90 (0.57, 1.41)	0.6

*Total number of patients interviewed was 451 in the control arm and 453 in the intervention arm.
†Adjusted for accredited drug dispensing outlet (ADDO) accreditation, number of customers at ADDO purchasing artemisinin-based combination therapies (ACTs) (< 20 vs. 20 or more), and patient education (patient or caregiver completed primary school).
‡Completed treatment unknown for three patients in the control arm and two patients in the intervention arm.
§Timely completion unknown for 10 patients in the control arm and 11 patients in the intervention arm.



[1]Reasons for non-adherence not given for 11 patients in control arm and 9 patients in intervention arm.

FIGURE 4. Reasons given by patients/caretakers for not completing treatment.

on patient adherence to antimalarial drugs. One study from 1998–2001 in Kilifi, Kenya found that trained shopkeepers were willing to take on an advisory role, resulting in both increases in advice and the proportion of patients taking adequate doses of chloroquine and sulfadoxine pyrimethamine or sulfadoxine-pyrimethamine.[14] Although receiving instructions has been associated with patient adherence to antimalarials in several studies in the public and private sectors,[11,39,40] other factors might also influence patient adherence, including patient education, higher socioeconomic status, treatment-seeking behavior, understanding the instructions, knowledge and perceptions of the illness or of the drug, and satisfaction with information received or with the drug.[5]

The private retail sector is likely to continue to be an important source of treatment of malaria and there is a need to maximize patient adherence to ACTs. Given the effectiveness of text message reminders on health worker case management in Kenya and the low cost of this intervention, there is potential for further evaluations of text message interventions targeted at dispensers in the private retail sector to improve dispenser knowledge, advice provided, and patient adherence, particularly in settings where dispensers have not received recent training on malaria. Such interventions should ensure message content addresses gaps in dispenser knowledge and would benefit from additional research on dispenser readiness to provide advice, and client receptivity to their advice. There should also be further consideration of how best to design the evaluation so that dispensers are motivated to communicate the importance of adherence without biasing study results.

The double gap between dispenser knowledge and providing advice and then patients receiving advice and being adherent may also call for other interventions to enhance adherence. Text message reminders to patients have been shown to be a low-cost approach to improve patient adherence to antiretroviral therapy for HIV[41–43] and have been used in two recent studies to increase patient adherence to malaria test results and treatment (Goldberg J, unpublished data).[44] However, scaling up a text message intervention targeted at malaria patients in Tanzania would require an increase in personal mobile phone use among patients most at risk of malaria,[45] as only about half of the households in rural areas own a mobile phone,[29] and the phone may be shared among household members. In contrast, nearly all dispensers censused in Mtwara regularly used at least one mobile phone.

Other interventions that have been shown to improve patient adherence to antimalarial drugs include packaging and community education.[46] ACTs are now mostly available in factory packaged unit dose packs blister packs with illustrated instructions, therefore additional room for improvement may be limited. One possible modification could be improved instructions in local languages. Community education through communication campaigns could be helpful in emphasizing the importance of taking all doses, but it may be challenging to communicate the details of when and how to take each dose to the general population. Finally, the introduction of mRDTs in the private sector might have positive implications for patient adherence, especially if also combined with dispenser advice.[5]

CONCLUSION

Text message reminders improved some aspects of dispenser knowledge of advice to provide to patients when dispensing AL in the private sector. However, patients in the intervention arm were not more likely to report receiving improved advice and did not have higher adherence than patients in the control arm. Adherence to AL among patients in both arms was suboptimal, highlighting the need for studies evaluating other interventions to improve adherence to ACTs obtained in the private retail sector.

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Authors' addresses: Katia Bruxvoort, Department of Global Health and Development and Department of Disease Control, London School of Hygiene and Tropical Medicine, London, UK, E-mail:

katia.bruxvoort@lshtm.ac.uk. Charles Festo, Admirabilis Kalolella, Peter Lyaruu, and Mitya Kenani, Ifakara Health Institute, Impact Evaluation Thematic Group, Dar es Salaam, Tanzania, United Republic of, E-mails: cfesto@ihi.or.tz, akalolella@ihi.or.tz, piere .lyaruu@yahoo.com, and mityamillie@yahoo.com. Matthew Cairns, London School of Hygiene and Tropical Medicine, Infectious Disease Epidemiology, London, UK, E-mail: matthew.cairns@lshtm.ac.uk. S. Patrick Kachur, CDC, Malaria Branch, Atlanta, GA, E-mail: spk0@cdc.gov. Catherine Goodman, London School of Hygiene and Tropical Medicine, Global Health and Development, London, UK, E-mail: catherine.goodman@lshtm.ac.uk. David Schellenberg, London School of Hygiene and Tropical Medicine, Department of Disease Control, London, UK, E-mail: david.schellenberg@lshtm.ac.uk.

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6 Adherence in the public and private retail sectors

6.1 Introduction

This chapter addresses the first research objective, comparing differences in patient characteristics and levels of adherence between patients obtaining AL in public health facilities and ADDOs, and examining factors associated with adherence in both of these settings. This paper reports results from the observational study in public health facilities in comparison with the control arm of the CRT described in the previous chapter.

In addition to the paper submitted to the Malaria Journal, Section 6.3 presents and discusses additional data that were not included in the submitted manuscript.

6.2 Research paper (cover sheet on next page)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Katia Bruxvoort
Principal Supervisor	David Schellenberg
Thesis Title	Evaluating patient adherence to artemether-lumefantrine obtained from public and private drug outlets in Tanzania

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Malaria Journal
Please list the paper's authors in the intended authorship order:	Katia Bruxvoort, Admirabilis Kalolella, Matthew Cairns, Charles Festo, Mitya Kenani, Peter Lyaruu, S. Patrick Kachur, David Schellenberg and Catherine Goodman
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had the primary role of designing the study, overseeing field work, analysing the data, and drafting the manuscript.

Student Signature: Katia Buxton **Date:** 14 Dec 2014

Supervisor Signature: [signature] **Date:** 15 Dec 14.

Are patients attending the public or private retail sector more likely to complete treatment? An analysis of patient adherence to artemether-lumefantrine in southern Tanzania

Katia Bruxvoort[1]

Corresponding author

Email: katia.bruxvoort@lshtm.ac.uk

Admirabilis Kalolella[2]

Email: akalolella@ihi.or.tz

Matt Cairns[1]

Email: matthew.cairns@ lshtm.ac.uk

Charles Festo[2]

Email: cfesto@ihi.or.tz

Mitya Kenani[2]

Email: mityamillie@yahoo.com

Peter Lyaruu[2]

Email: piere.lyaruu@yahoo.com

S Patrick Kachur[3]

Email: spk0@cdc.gov

David Schellenberg[1]

Email: david.schellenberg@lshtm.ac.uk

Catherine Goodman[1]

Email: catherine.goodman@lshtm.ac.uk

[1] London School of Hygiene and Tropical Medicine, London, UK

[2] Ifakara Health Institute, Dar es Salaam, Tanzania

[3] Malaria Branch, Centers for Disease Control and Prevention, Atlanta, USA

Abstract

Background

Artemisinin combination therapy (ACT) is first-line treatment for malaria in the public sector of most endemic countries and increasingly available in the private sector. Most studies on ACT adherence have been conducted in the public sector, with minimal data from private retailers.

Methods

Parallel adherence studies were conducted in Mtwara, Tanzania, in which patients obtaining artemether-lumefantrine (AL) at 40 randomly selected public health facilities and 37 accredited drug dispensing outlets (ADDOs) were followed up at home and questioned about each dose taken. The effect of health sector on adherence, controlling for potential confounders was assessed using logistic regression with a random effect for outlet.

Results

Of 572 health facility patients and 450 ADDO patients, 74.5% (95% CI: 69.8, 78.8) and 69.8% (95% CI: 64.6, 74.5), respectively, completed treatment and 46.0% (95% CI: 40.9, 51.2) and 34.8% (95% CI: 30.1, 39.8) took each dose at the correct time ('timely completion'). ADDO patients were wealthier, more educated, older, sought care later in the day, and were less likely to test positive for malaria than health facility patients. Controlling for patient characteristics, the adjusted odds of completed treatment and of timely completion for ADDO patients were 0.65 (95% CI: 0.43, 1.00) and 0.69 (95% CI: 0.47, 1.01) times that of health facility patients. Higher socio-economic status was associated with both adherence measures. Higher education was associated with completed treatment (adjusted OR=1.68, 95% CI: 1.20, 2.36); obtaining AL in the evening was associated with timely completion (adjusted OR=0.35, 95% CI: 0.19, 0.64). Factors associated with adherence in each sector were examined in separate models. In both

public and private sectors, recalling correct instructions was positively associated with both adherence measures. In health facility patients, but not ADDO patients, taking the first dose of AL at the outlet was associated with timely completion (adjusted OR=2.11, 95% CI: 1.46, 3.04).

Conclusion

When controlling for patient characteristics, there was some evidence that the adjusted odds of completed treatment and timely completion for ADDO patients was lower than that for public health facility patients. Better understanding is needed of which aspects of patient care are most important for adherence, including the role of effective provision of advice.

Keywords Malaria, ACT, adherence, public health facilities, private sector, ADDOs

Background

As artemisinin-based combination therapy (ACT) for malaria becomes widely available, patient adherence to the full course of treatment is increasingly important to ensure positive clinical outcomes and minimize the selection of drug-resistant parasites [1-3]. ACT is the first-line treatment for *Plasmodium falciparum* malaria in most malaria-endemic countries and has become increasingly available in the private retail sector, where many patients seek care for malaria [4-9].

Estimates of patient adherence to ACT range from 39 to 100%, reflecting both variation in patient characteristics, interaction with providers, study settings, differences in study procedures, and methods of assessing adherence [10, 11]. The vast majority of studies designed to measure adherence have been conducted in the public sector, while a few studies have used household survey data to assess adherence from mixed community sources [12-17]. Only one study had specifically addressed patient adherence to ACT obtained in the private sector. This study, conducted in a convenience sample of four shops in a single Ugandan district where subsidized ACT had been made available through a pilot programme, reported that 66% of patients seeking treatment completed the full course of ACT [18].

As access to ACT increases, there is a need to understand levels and determinants of patient adherence in both public and private sectors, in order to design and target appropriate interventions. Patients seeking care in the private retail sector may have different characteristics (e.g., age, socio-economic status, illness severity, etc.) than patients who seek care in public

health facilities [7, 19, 20], though some patients seek care in both sectors. Similarly, provider characteristics (e.g., training, communication, reputation, costs, drug availability, motivation, etc.) may also vary and affect where patients seek care [7, 21]. It is unclear how these differences affect patient adherence.

In Tanzania, artemether-lumefantrine (AL) for treatment of uncomplicated malaria was first rolled out to public health facilities in 2006. The recommended treatment regimen is six doses of AL over three days, with one to four tablets (20 mg artemether/120 mg lumefantrine) per dose depending on the patient's weight/age band. National guidelines state that the first dose should be taken under observation of the dispenser, the second dose eight hours after the first dose, and the remaining doses morning and evening of the second and third days [22]. Treatment at public health facilities for children under five years of age and pregnant women is intended to be free of charge, but this policy is not always followed [20].

Treatment for malaria in the private sector in Tanzania is sought at private health facilities, pharmacies, drug shops, and general stores. More than two-thirds of anti-malarial drug sales from private for-profit providers occur in drug shops [23], many of which have been upgraded through the accredited drug dispensing outlet (ADDO) programme. ADDOs were first piloted in 2003 in order to improve availability, quality, and affordability of pharmaceutical services in rural and peri-urban areas without pharmacies. ADDOs have now been rolled-out nationwide, with an estimated 9,000 ADDOs serving the 25 regions of mainland Tanzania [24]. The ADDO programme involves multiple components including training, accreditation, and regulatory oversight by trained inspectors [24-26]. Dispensers are required to have a health qualification of

a nurse assistant or higher and must attend a six-week training course on topics such as business practices, regulations, record-keeping, use of ADDO-approved medicines, dispenser ethics and communication skills. ADDOs are allowed to sell a limited number of prescription-only drugs, including an approved list of antibiotics and antimalarial drugs. Availability of ACT was limited in ADDOs until the implementation of the Affordable Medicines Facility- malaria (AMFm) in 2010, which led to a significant reduction in price and a corresponding increase in availability [23, 27].

This paper reports results of two parallel, contemporaneous studies in southern Tanzania to compare patient adherence to ACT obtained in public health facilities with adherence to ACT obtained from ADDOs in the same area and to examine factors associated with adherence in each sector.

Methods

Study setting

The studies were conducted in Mtwara, a rural region in southeastern Tanzania with more than a third of the population in the lowest national wealth quintile [28]. In 2012, malaria prevalence in Mtwara in patients of all ages seeking care for febrile illness was 15% among patients attending ADDOs and 32% among patients attending public health facilities [29, 30]. Conversion of drug shops to ADDOs in Mtwara commenced in 2006, with all drug shops in Mtwara officially required to have upgraded to ADDO status by 2011. At the time of the study, some shops had not

yet paid fees, received training, or been visited by inspectors but were tolerated as 'prospective ADDOs' (in this paper the term ADDOs is used to include both accredited outlets and 'prospective ADDOs'). To support the increased availability of ACT in ADDOs, the government offered a one-day training that included treatment of malaria with ACT to dispensers with previous nursing training in Mtwara in August 2011.

Study design

In health facilities, a descriptive study was conducted to assess patient adherence to AL. The study in ADDOs was designed as part of a cluster-randomized trial to evaluate a text message intervention to improve dispenser knowledge of advice to provide to patients obtaining AL. Details of the intervention and results of the trial are presented separately [31]. Only data from the control arm, which did not receive any intervention, are presented here.

Sample size calculations

The target sample size for ADDO patients was based on the text message intervention trial [31], and a similar sample size was desired for public health facilities within the constraints of study resources. Based on adherence previously reported among patients obtaining ACT at public health facilities in Tanzania, which ranged from 75 to 98% [32-34], adherence among patients attending public health facilities was expected to be 75%, with lower adherence among patients attending ADDOs (60%). Assuming a hypothesized design effect of 2.5 and 20% loss to follow-up, 448 registered patients from 36 outlets in each sector (approximately 12 to 13 patients per outlet) would have 80% power to detect this difference with 95% confidence. Given the lower design effect observed in the study (1.5) and more interviewed patients than anticipated, the

study was powered to detect a 10 percentage point difference between sectors, but was not able to detect if a smaller difference in completion rates between sectors was due to random error.

Selection of outlets

A list of all public dispensaries and health centres in Mtwara, excluding district hospitals, was compiled by visiting each district and interviewing the district medical officers. The health facilities were randomly ordered, and the first 40 health facilities were selected. Sampling of ADDOs was based on a census in Mtwara of all ADDOs, including prospective ADDOs, conducted prior to the text message intervention trial. From this list, ADDOs were selected sequentially at random, with all ADDOs within 400 m of a selected ADDO, or any ADDO where staff from a selected ADDO also worked, removed from the sampling frame. Forty ADDOs were randomized to the control arm [31].

Study procedures

From September through November 2012, dispensers at selected public health facilities and ADDOs were visited by study supervisors and given a standard introduction about study objectives. In order to limit patients' awareness of the primary interest in adherence, which could have led to a biased assessment, dispensers were told the focus was how patients chose to treat fever and that some, but not all, patients would be visited at their homes. Dispensers were asked to fill out a registration form for all patients dispensed any treatment for fever, including day and time of the visit, the patient's name, drugs dispensed, and a description of where the patient lived. Dispensers were provided with blister packs of AL to be dispensed in public health facilities to patients prescribed ACT, and in ADDOs to patients indicating an intention to

purchase treatment for malaria. Study staff visited outlets every day to check and collect registration forms. While the intention had been to register 12 patients obtaining ACT for one week per outlet, the protocol was adjusted due to low attendance at some outlets to register all patients obtaining ACT for two to three weeks per outlet.

Eligible patients who obtained AL were identified from the registration forms and assigned patient identification numbers. Patients were visited at their homes three days later (day 4), and all attempts to locate and interview patients were recorded. Where written informed consent was given, patients or their caregivers were asked about demographic and socio-economic characteristics, treatment-seeking history, symptoms, and detailed information about each dose of AL taken. Patients were asked if dispensers provided each of several aspects of advice on AL (e.g., number of pills to take per dose, when to take second dose, etc.), and if so, what advice was given. Blister packs were also requested for a pill count. Since the *P. falciparum* histidine-rich protein II (HRP-2) persists in the blood following treatment, HRP-2-based malaria rapid diagnostic tests (mRDTs) (Pf-specific from ICT Diagnostics, Cape Town, South Africa) were conducted to indicate infection prior to treatment. Blood smears were collected to detect infection at the time of interview. Blood smears were stained in the field and transported to the Ifakara Health Institute, where they were double-read by two microscopists blinded to results from each other and the mRDT, with discrepant readings resolved by a third microscopist.

Adherence was defined in two ways [10]. Patients were considered to have verified completed treatment if they reported taking all doses by the time of the interview and, when available, a pill count verified that no pills remained in the blister pack. Where blister packs were not available,

self-report alone determined if patients completed treatment. The second, more stringent definition included a time component, based on patient reports of the time each dose was taken using the Swahili times of day: *alfajiri* (early morning), *asubuhi* (morning), *mchana* (afternoon), *jioni* (evening), *usiku* (night), and *usiku sana* (late night). Patients were considered to have verified timely completion if they took the correct number of pills for each dose, and took the second dose at the Swahili time of day corresponding with eight hours after the first dose, followed by taking each of the remaining doses at the Swahili time of day corresponding with 12 hours after the previous dose, verified when possible by the absence of pills in the blister pack. The terms completed treatment and timely completion are hereafter used to refer to these definitions.

Data entry and analysis

All patient and dispenser interview data were collected using personal digital assistants, and data extracted from study forms (census, registration and follow-up forms) were double entered into Microsoft Access databases. Data were analysed in Stata 11.0 (Stata Corporation, College Station, USA). Robust standard errors were used for percentages and 95% confidence intervals, with p-values reported for the Pearson design-based F test. Wealth quintiles describing socio-economic status were assigned to patients based on standard Demographic and Health Survey variables, using principal components analysis of the pooled sample of public health facility and ADDO patients [28]. Two analyses of factors associated with adherence were conducted: (i) a comparison of adherence between the public and private sectors controlling for patient characteristics; and, (ii) an analysis within each sector exploring the association of adherence with factors related to the care received at the outlet and patient characteristics.

Comparison of adherence between sectors

In the analysis on the impact of sector on patient adherence, random effects logistic regression was used for both completed treatment and timely completion to compare the odds of adherence between private sector ADDO patients and public sector health facility patients, adjusting for patient characteristics identified *a priori* (age group, education and time between obtaining AL and interview) or those that made important changes to the odds ratio for sector in bivariate models. In this analysis, no adjustment was made for variables related to care received at the outlet (e.g., taking first dose at outlet, recalling correct instructions on how to take AL, etc.), as these factors might mediate the effect of sector (i.e., lie on the causal pathway between sector and adherence).

Factors associated with adherence within sectors

Within each sector, the association of variables related to care received at the outlet with 1) completed treatment, and, 2) timely completion was explored in univariate and multivariate models. Logistic regression with robust standard errors was used, as checks showed that the quadrature approximations for random effects models were not reliable. Patient characteristics and care-related variables that were associated with completed treatment or timely completion in either sector in unadjusted analyses were included in all four multivariate models.

Ethics

All questionnaires, consent forms and other study documents were translated into Swahili and piloted prior to use. Written informed consent was collected from dispensers prior to census,

patient registration, and interview and from patients or their caregivers prior to interview. The study protocol was approved by the ethical review boards of Ifakara Health Institute and London School of Hygiene and Tropical Medicine. CDC advisors provided technical assistance in design and analysis but were not engaged in data collection and did not have access to personal identifiers.

Results

Patient characteristics, care received, and status at interview

Data were collected from patients obtaining AL at all 40 selected health facilities and 37 of 40 selected ADDOs, with three ADDOs closed or refusing to participate. Of 604 registered health facility patients obtaining AL (median=16 patients per outlet, range two to 32), 572 patients (95%) were interviewed. From ADDOs, 537 patients obtaining AL were registered (median=17 patients per outlet, range one to 29), and 450 patients (84%) were interviewed. The most common reasons in both sectors for non-completion of interviews were not locating the patient's home (38% at public facilities and 43% at ADDOs), or the patient having travelled out of the study region (28 and 16%).

Characteristics of patients differed between sectors (Table 1). ADDO patients were more likely to be male and older than those attending public health facilities. ADDO patients/caregivers were wealthier, with 32% in the least poor wealth quintile compared to 10% of public health facility patients, and were more likely to have finished primary school (72 *vs* 58%, p=0.007). Over a

third of patients in both sectors had previously sought care for their illness episode, many of whom had gone to a general store/kiosk or taken drugs stored at home or from a neighbour. Reported symptoms were similar across outlet type, except more patients from public health facilities had experienced respiratory symptoms (14 *vs* 7.5%, p=0.007) and more ADDO patients had experienced body pain (30 *vs* 15%, p<0.0001) or fatigue (18 *vs* 10%, p=0.003), with few patients in either sector reporting convulsions or other signs of severe disease. ADDOs were much more likely than public health facilities to be located in urban areas, but outlets in both sectors were attended mostly by patients living within 2.5 km (about half-an-hour walk) from the outlet. ADDO patients were also more likely to have obtained AL later in the day, reflecting the fact that most public health facilities in Mtwara close for outpatient services by mid-afternoon, while ADDOs often stay open through the evening. Because of this, the day-4 interview was more likely to occur earlier (between 60-67 hours from the time the drug was obtained) for ADDO patients than for public health facility patients (26 *vs* 6%).

Table 2 compares care received at the outlet and patient status at interview for each sector. Half of the public health facility patients reported being tested for malaria, while 11% reported being tested in ADDOs, where diagnostic tests for malaria had not been officially introduced. Public health facility patients were slightly more likely to be told a diagnosis (64 *vs* 54%, p=0.051) and more likely to take the first dose of AL immediately at the outlet (41 *vs* 10%, p<0.0001), while ADDO patients were more likely to pay for AL (98 *vs* 29%, p<0.0001). Similar percentages of patients using outlets in both sectors reported receiving advice on how to take AL from the dispenser, with 60% able to recall correct instructions on the number of pills per dose, number of doses per day, and number of days to take AL. Approximately 60% of patients in both sectors

reported being told to take the second dose of AL after eight hours and to take each dose with food or milk. Public health facility patients were more likely to recall being told to finish all doses even if feeling better (78 *vs* 63%, p=0.0006). However, less than 5% of patients treated in either sector reported being advised on possible side effects or on what to do in case of vomiting within half-an-hour of taking a dose.

At the time of interview, approximately 14% of both public health facility and ADDO patients reported a current fever and 92% could play or work. More patients who had attended public health facilities tested positive by the mRDT performed by study staff during the interview (50% compared to 28% of ADDO patients, p=0.001). However, by reference blood smear, indicating current infection status at the time of interview, only 2.9% of public health facility patients and 1.4% of ADDO patients were positive (p=0.1).

Comparison of adherence between sectors

Among public health facility patients, 74.5% (95% CI: 69.8, 78.8) completed treatment, compared with 69.8% (95% CI: 64.6, 74.5) among ADDO patients (p=0.2). Timely completion was much lower and differed between sectors, with 46.0% (95% CI: 40.9, 51.2) of public health facility patients and 34.8% (95% CI: 30.1, 39.8) of ADDO patients taking the correct number of pills at the correct time of day for each dose (p=0.003). Variables that made important differences to the odds ratio for sector in the bivariate models were wealth quintile, distance from home to outlet, and time of day AL was obtained, and these were included along with age group, patient/caregiver education, and time between obtaining AL and interview in the models comparing adherence between sectors. Patients in the two least poor wealth quintiles had higher

adjusted odds of both measures of adherence compared to those in the poorest wealth quintile (Table 3). The adjusted odds of completed treatment for those who had finished primary school was 1.68 times that of patients who had not (95% CI: 1.20, 2.36; p=0.003), but there was no evidence of an association with timely completion (aOR=1.06, 95% CI: 0.77, 1.75; p=0.9). Compared to patients who obtained AL in the morning, patients who obtained AL in the evening were similarly likely to complete treatment (aOR=0.93, 95% CI: 0.50, 1.70; p=0.8), but had much lower adjusted odds of timely completion (aOR=0.35, 95% CI: 0.19, 0.64; p=0.001). Furthermore, patients interviewed a longer time after obtaining AL (68-72 hours, 73-84 hours, and 85 hours or more) had higher adjusted odds of completed treatment and timely completion than patients visited 60-67 hours after obtaining AL (Table 3). When controlling for these patient characteristics, the adjusted odds of completed treatment for ADDO patients was 0.65 times the odds of completed treatment for public health facility patients (95% CI: 0.43, 1.00; p=0.048), and the adjusted odds of timely completion for ADDO patients was 0.69 that of health facility patients (95% CI: 0.47, 1.01; p=0.056).

Factors associated with adherence within sectors

Unadjusted associations of patient characteristics and care received at the outlet with completed treatment and timely completion are presented for each sector in Additional files 1-2. Variables not associated with either adherence measure in either sector, such as patient sex, having sought previous treatment, report of specific symptoms, and paying for AL, were not included in the sector specific multivariate analyses shown in Table 4. In contrast with the analyses comparing the effect of sector on adherence, in these sector specific models there were no clear patterns of association between education and socioeconomic status and either measure of adherence.

Similar to the previous analysis for the effect of sector, patients obtaining AL in the afternoon or in the evening had lower adjusted odds of timely completion than those obtaining AL in the morning, although this was the case only in public health facilities. In both public health facilities and ADDOs, longer time between obtaining AL and interview were again strongly associated with completed treatment. However, there was no evidence of an association with timely completion in public health facilities, and in ADDOs only being interviewed 72-84 hours after obtaining AL (not 68-72 hours or 85 hours or more) compared to 60-67 hours was associated with timely completion. In addition, public health facility patients, but not ADDO patients, sleeping under a bed net the night before the interview, having experienced fever symptoms, and living within 2.5 km of the outlet was associated with completed treatment, while seeking care within two days of fever onset was associated with timely completion.

Factors related to care received at the outlet varied by sector in their associations with both adherence measures (Table 4). In the public sector, reporting being tested for malaria at the outlet was not associated with completed treatment (aOR=1.30, 95% CI: 0.82, 2.04; p=0.3), but there was weak evidence of an association with timely completion (aOR=1.47, 95% CI: 0.96-2.29; p=0.078). Among ADDO patients, however, the adjusted odds of completed treatment and timely completion were lower for those who reported being tested compared to those who did not report being tested (aOR=0.39, 95% CI: 0.17-0.85; p=0.018 and aOR=0.48, 95% CI: 0.24, 0.97; p=0.041). There were no evident associations of taking the first dose of AL at the outlet with completed treatment in either sector or timely completion in ADDO patients, but the adjusted odds of timely completion were higher among health facility patients who took the first dose of AL at the outlet (aOR: 2.11, 95% CI: 1.46, 3.04; p<0.001). Recalling correct instructions

given by the dispenser on the AL regimen was strongly associated with both measures of adherence in public health facility and ADDO patients. In public health facilities, reporting that the dispenser used the packaging as a visual aid to explain how to take AL was also associated with timely completion (aOR=1.77, 95% CI: 1.12, 2.80; p=0.022). In addition, the adjusted odds of timely completion among ADDO patients who recalled being told to take the second dose after eight hours were 1.77 times that of their counterparts (95% CI: 1.12, 2.80; p=0.015), but recalling this advice was not associated with either measure of adherence in public health facility patients. Reporting being told to complete all doses of AL even if feeling better was also not associated with either adherence measure, except for a lower adjusted odds of timely completion in public health facility patients (aOR=0.44, 95% CI: 0.28, 0.70; p=0.001).

Discussion

This study indicates that patients seeking care for malaria at public health facilities and ADDOs in southern Tanzania have different characteristics, with those attending ADDOs more likely to be older, more educated, wealthier, and seeking treatment later in the day. Although similar proportions of patients from both sectors completed treatment, the proportion of patients taking each dose at the correct time (timely completion) was lower in ADDO patients. When controlling for patient characteristics, there was some evidence that the adjusted odds of completed treatment and timely completion were lower in ADDO patients compared to public health facility patients.

Completed treatment and timely completion among patients from public health facilities were 75 and 46%, respectively, comparable to other studies under real-life conditions (i.e., not clinical trials) in the public sector, which had found completed treatment verified by pill count of 64-77% and timely completion verified by pill count of 39-75% [10], including one study from Tanzania [32]. Another study from the public sector in Tanzania recently reported lower timely completion (14.9%) [35], while two other studies using different definitions and study designs found higher adherence (88.3 and 90%) [33, 34]. In ADDOs, completed treatment verified by pill count was 70%, comparable to the 66% adherent by the same definition in the study by Cohen *et al.* in the private retail sector in Uganda [18].

Characteristics related to care received at the outlet differed between sectors, with health facility patients more likely to be tested for malaria at the outlet, be told their diagnosis, take the first dose of AL at the outlet, and receive advice on completing treatment even if feeling better. However, there was no difference between sectors in other advice patients reported receiving. It is possible that advice provision in Mtwara region may have been superior to that in other regions, as ADDOs in Mtwara and Lindi regions received a one-day training, including ACT treatment, in 2011. In the sector-specific models, some differences between sectors were observed in the association of these characteristics with completed treatment and timely completion, although caution in interpretation is needed given the number of comparisons made in the analyses. For example, in public health facilities, obtaining a malaria test at the outlet was not associated with completed treatment or timely completion. However, in ADDOs, patients who reported obtaining a malaria test appeared to be less adherent by both measures. One explanation for this contrast might be the status of mRDT roll out, which had occurred in public

health facilities in Mtwara several months prior to the study, whereas ADDOs were not officially permitted to use mRDTs, and only 50 patients (11%) reported being tested (compared to 275 (54%) in public health facilities). The difference is not explained by reported test results, as 96% of patients reporting a malaria test in both sectors reported a positive result, though only 70% of tested health facility patients and 35% of tested ADD0 patients had a positive study mRDT at interview.

At public health facilities, taking the first dose of AL at the outlet was associated with timely completion, but not completed treatment. In ADDOs, where less than 10% of patients took the first dose at the outlet, there was no evidence of an association with either measure of adherence. Taking the first dose at the outlet might improve adherence by providing a model for patients or caregivers on how to take treatment, generating more communication with patients, or improving their confidence to complete the remaining doses at home. In addition, patients in both sectors who recalled correct instructions on how to take AL had much higher odds of completing treatment and timely completion than patients who did not recall correct instructions. This highlights the importance of clear instructions for achieving adherence [36]. A review of the previous literature shows considerable variation in factors associated with adherence to anti-malarials, but provision of better information on how to take drugs has been an important factor in more than one study [10]. Alternatively, patients who are more conscientious about their treatment may also be more likely to recall instructions. Another factor that might affect adherence but was not assessed reliably in this study is the attendance of the patient at the outlet, which is required to obtain treatment at public health facilities but not at ADDOs. Patients who received advice second-hand could be less likely to adhere. However, this should not affect the

comparison between sectors, as whether or not the patient attended the outlet might lie on the causal pathway between sector and adherence, similar to the other variables related to care received at the outlet. Other factors that were not assessed, related to patient understanding of treatment or respect for dispensers, might also be important in explaining adherence.

Timely completion was 30-35 percentage points lower than completed treatment, even though timeliness of doses was based on times of day rather than exact times. While there is consensus that ACT will only be effective if taken correctly, the importance for treatment effectiveness of the recommended time intervals between doses is less clear. In this study, only 46% of public health facility patients and 35% of ADDO patients completed all doses at the recommended intervals, and there was no association between study mRDT positivity at interview (indicating malaria infection at care seeking) and adherence. While 50% of health facility patients and 28% of ADDO patients were positive by study mRDT at interview, only 22 patients overall (approximately 2%) were positive by reference blood smear, suggesting that most patients who had been malaria positive at the time of care seeking may have been treated effectively, even though only half of these had completed all doses at the correct time. However, blood smears may not capture all submicroscopic parasitaemia present at day 4, although these could lead to subsequent treatment failure [37].

The dosing regimen for AL in national guidelines states that doses should be taken at 0, 8, 24, 36, 48, and 60 hours, but for practical reasons a simpler regimen is recommended, illustrated by pictograms on packaging, which assume that patients obtain AL in the morning, take the second dose later the same day, followed by the remaining doses morning and evening for two more

days [22]. More patients from ADDOs than public health facilities had obtained AL later in the day, as ADDOs had longer operating hours than public health facilities. Patients who obtained AL in the evening in the analysis for the effect of sector, and public health facility patients who obtained AL in the afternoon or evening, had lower adjusted odds of timely completion than patients obtaining AL in the morning. If eight hours after the first dose falls in the middle of the night, patients may not wake up to take the second dose, and they may be unsure when to take the remaining doses. Modified recommendations and pictograms for patients obtaining AL in the evening may be helpful in improving adherence, but this depends on establishing a clearer basis for the importance of the timing of dose intervals.

This study has several limitations. Patients may have altered their behaviour if they became aware of a potential visit or study objectives. In an attempt to prevent this, information given to dispensers was limited, visits of study research assistants to the outlets were minimized, and the study was conducted in a large number of outlets, each for a short period of time. The data presented here are also based primarily on patient self-report, which is susceptible to recall bias and social desirability bias, if patients did not remember when each dose was taken or provided the expected responses in order to avoid being seen as negligent. In addition, patients' consultations with dispensers were intentionally not observed to avoid influencing behaviour. Instead patients' reports of care and advice received were analysed, though recall may not have been accurate or advice of good quality. While dispensers' characteristics and knowledge of advice to provide to patients were reported as part of the intervention study in ADDOs [31], interviews of dispensers were not conducted in health facilities, and it was therefore not possible

to assess the impact of these factors across the sectors. Similarly, there may have been other important patient or care-related factors that were not assessed.

This study was conducted in the context of AFMm-subsidized ACT, and the median cost of AL in ADDOs was low (approximately $0.04 per tablet, or $0.84 for an adult equivalent treatment dose). In a setting without AL subsidies, adherence could vary. One could argue that lower adherence in ADDO patients could be a reason not to continue a subsidy of ACT in these outlets. However, the differences in adherence levels were not very large and the reasons for the differences remain unclear. Moreover, even if subsidized ACTs were not available in ADDOs (as was previously the case) patients would likely continue to seek care at these outlets, but obtain less effective antimalarials. Thus, improving care for malaria at both ADDOs and public health facilities should be a priority.

Conclusion

Similar proportions of patients dispensed ACT from public health facilities and ADDOs completed treatment, but the proportion with timely completion was lower in ADDO patients. Characteristics of patients obtaining ACT differed between sectors. When controlling for patient characteristics, there was some evidence that the adjusted odds of completed treatment and timely completion for ADDO patients was lower than that for public health facility patients. Further studies are necessary to understand and improve the impact of patient care on adherence, including the role of effective provision of advice.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

KB, AK, MC, SPK, DS, and CG designed the study. KB, AK, CF, MK, and PL planned and oversaw fieldwork. KB, CF and MC cleaned and analysed data. KB, MC, SPK, DS, and CG interpreted results. KB wrote the first draft of the manuscript. All authors approved the final manuscript.

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Table 1 Patient characteristics by sector (%, 95% CI)

	Public health facilities (N=572 patients from 40 outlets)	Private ADDOs (N=450 patients from 37 outlets)	p-value
Male	43.2 (39.9, 46.5)	53.1 (46.8, 59.4)	0.007
Age[1]			
Under 3 years	42.5 (37.4, 47.8)	18.2 (14.5, 22.6)	
3 years to under 8 years	28.2 (23.5, 33.3)	23.1 (18.8, 28.0)	
8 years to under 12 years	6.6 (4.3, 10.0)	9.1 (6.9, 12.0)	
12 years and above	22.7 (18.7, 27.3)	49.6 (43.0, 56.2)	<0.0001
Patient (or caregiver if patient below age 12) completed primary school[2]	58.2 (50.7, 65.4)	71.8 (65.2, 77.6)	0.007
Socio-economic status[3]			
1st quintile (most poor)	27.9 (23.1, 33.2)	10.2 (7.6, 13.5)	
2nd quintile	24.5 (20.5, 29.1)	14.2 (10.1, 19.8)	
3rd quintile	20.0 (16.5, 23.9)	20.2 (15.4, 26.1)	
4th quintile	17.3 (13.1, 22.6)	23.3 (19.5, 27.6)	
5th quintile (least poor)	10.3 (7.4, 14.4)	32.1 (23.3, 42.2)	<0.0001
Slept under net the night before the interview	73.6 (68.9, 77.8)	71.4 (65.3, 76.9)	0.6
Sought care for this episode prior to attending outlet	36.4 (31.9, 41.2)	37.8 (31.6, 44.4)	0.7
Sought care at outlet within two days of fever onset[4]	77.5 (73.5, 81.1)	72.0 (67.8, 75.9)	0.051
Symptoms			
Fever or headache	94.1 (91.3, 96.0)	91.1 (87.6, 93.7)	0.1
Respiratory	14.0 (10.5, 18.4)	7.5 (5.3, 10.7)	0.007
Stomach upset	53.5 (47.7, 59.2)	48.9 (42.3 55.6)	0.3
Body/joint pain	15.4 (12.2, 19.1)	30.4 (25.2, 36.2)	<0.0001
Fatigue	10.1 (7.5, 13.6)	18.0 (14.2, 22.5)	0.003
Convulsions	2.5 (1.6, 3.9)	0.4 (0.1, 1.7)	0.007
Other[5]	12.4 (9.6, 15.9)	10.0 (7.5, 13.1)	0.2
Attended an outlet in an urban ward	13.1 (5.1, 29.6)	68.4 (48.3, 83.4)	<0.0001
Distance of 2.5 km or less from home to outlet (by GPS coordinates[6])	69.4 (62.6, 75.4)	71.4 (58.5, 81.5)	0.8
Time of day drug was obtained			
Morning	77.1 (71.9, 81.6)	44.7 (38.2, 51.3)	
Afternoon	18.7 (14.6, 23.6)	26.9 (22.2, 32.2)	
Evening	4.2 (2.5, 7.0)	28.4 (21.6, 36.4)	<0.0001
Time between obtaining AL and interview (hours)[7]			
60-67	5.8 (3.8, 8.6)	24.8 (20.7, 29.3)	
68-72	47.0 (41.7, 52.4)	37.4 (33.1, 41.9)	
73-84	32.5 (28.5, 36.7)	21.6 (16.9, 27.2)	
85 or more	14.7 (11.4, 18.8)	16.2 (12.1, 21.4)	<0.0001

[1]Age categories based on recommended age breakdown for AL blister packs in Tanzania.
[2]Caregiver education missing for five public health facility patients.
[3]Wealth quintiles pooled for public health facilities and ADDOs using principal component analysis of sampled patients based on standard Demographic and Health Survey variables. Data missing for one public health facility patient.
[4]Number of days since illness onset missing for 3 public health facility patients and 11 ADDO patients.
[5]Includes dizziness, crying/fussiness, startling (*kustukastuka*), sleep-talking (*kuweweseka*), worms, fast heart rate, stays in sun, red/inflamed eyes, and sores/ulcers.
[6]GPS data missing from 30 public health facility patients and 52 ADDO patients.
[7]Rounded to nearest hour. Data missing for 15 public health facility patients and 6 ADDO patients.

Table 2 Care received at outlet and patient status at interview by sector (%, 95% CI)

	Public health facilities (N=572 patients from 40 outlets)	Private ADDOs (N=450 patients from 37 outlets)	p-value
Treatment received at outlet			
Tested for malaria	54.4 (40.3, 67.9)	11.1 (8.0, 15.4)	<0.0001
Told diagnosis	64.1 (56.3, 71.1)	53.5 (46.1, 60.8)	0.051
Obtained correct blister pack for age[1]	78.9 (74.7, 82.5)	83.1 (78.7, 86.8)	0.1
Paid for AL	28.7 (24.0, 34.0)	97.8 (96.1, 98.7)	<0.0001
Took first dose of AL at outlet	40.7 (29.8, 52.7)	9.6 (6.3, 14.2)	<0.0001
Recall of instructions received from dispenser			
Recalled correct instructions given by dispenser on the number of pills per dose, number of doses, and number of days to take AL	60.8 (56.4, 65.2)	59.3 (53.7, 64.7)	0.7
Recalled that dispenser used packaging as a visual aid to explain how to take AL	85.6 (81.9, 88.6)	82.9 (77.9, 86.9)	0.3
Reported being told to take the second dose of AL eight hours after the first dose	58.0 (51.3, 64.5)	63.3 (57.9, 68.4)	0.2
Reported being told to take AL with food or milk	63.8 (57.9, 69.3)	61.8 (54.6, 68.5)	0.7
Reported being told to complete all doses of AL even if feeling better	77.9 (73.5, 81.7)	63.3 (55.7, 70.4)	0.0006
Reported being told to take a replacement dose in case of vomiting within half hour of taking a dose	1.9 (1.1, 3.5)	2.4 (1.3, 4.6)	0.6
Reported being told about possible side effects	2.3 (1.3, 4.0)	3.0 (1.6, 5.6)	0.6
Health status at interview			
Reported current fever at time of interview	13.7 (10.5, 17.7)	14.7 (11.1, 19.1)	0.7
Could play or work at time of interview	92.6 (89.2, 95.1)	92.4 (89.7, 94.5)	0.9
Tested positive by mRDT at interview[2]	49.6 (39.7, 59.5)	27.9 (20.7, 36.6)	0.001
Tested positive by blood smear collected at interview[3]	2.9 (1.7, 4.7)	1.4 (0.6, 3.0)	0.1
Adherence to AL			
Adherent by 'verified completed treatment'[4]	74.6 (69.8, 78.8)	69.8 (64.6, 74.5)	0.2
Adherent by 'verified timely completion'[5]	46.0 (40.9, 51.2)	34.8 (30.1, 39.8)	0.003

[1]Age categories based on recommended age breakdown for AL blister packs in Tanzania.
[2]mRDT data missing for 7 public health facility patients and 17 ADDO patients.
[3]Blood smear data missing for 15 public health facility patients and 18 ADDO patients.
[4]Patient completed all doses, verified by pill count when available. Data missing for 2 public health facility patients and 3 ADDO patients.
[5]Patient completed each dose at correct time with the correct number of pills per dose, verified by pill count when available. Data missing for 13 public health facility patients and 10 ADDO patients.

Table 3 Effect of sector on adherence controlling for potential confounders[1]

	Verified completed treatment[2]		Verified timely completion[3]	
	Adjusted odds ratio	p-value	Adjusted odds ratio	p-value
Attended ADDO vs. public health facility	0.65 (0.43, 1.00)	0.048	0.69 (0.47, 1.01)	0.056
Age[4]				
Under 3 years (ref)	---	---	---	---
3 years to under 8 years	1.01 (0.67, 1.52)	0.9	0.88 (0.61, 1.28)	0.5
8 years to under 12 years	1.07 (0.57, 2.09)	0.8	1.12 (0.62, 2.01)	0.7
12 years and above	1.02 (0.56, 2.05)	0.8	0.87 (0.60, 1.27)	0.5
Patient (or caregiver if patient below age 12) completed primary school	1.68 (1.20, 2.36)	0.003	1.06 (0.77, 1.45)	0.9
Socio-economic status[5]				
1st quintile (most poor, ref)	---	---		
2nd quintile	0.98 (0.62, 1.57)	0.9	1.04 (0.66, 1.64)	0.9
3rd quintile	1.17 (0.73, 1.88)	0.5	1.10 (0.70, 1.75)	0.7
4th quintile	2.25 (1.33, 3.81)	0.003	1.64 (1.03, 2.65)	0.039
5th quintile (least poor)	2.24 (1.28, 3.81)	0.005	2.34 (1.40, 3.93)	0.001
Distance from home to outlet within 2.5 km by GPS	1.30 (0.92, 1.85)	0.2	1.20 (0.87, 1.66)	0.3
Time of day drug was obtained				
Morning (ref)	---	---	---	---
Afternoon	0.96 (0.62, 1.47)	0.8	0.70 (0.48, 1.03)	0.070
Evening	0.93 (0.50, 1.70)	0.8	0.35 (0.19, 0.64)	0.001
Time between obtaining AL and interview (hours)				
60-67 (ref)	---	---	---	---
68-72	2.43 (1.39, 4.23)	0.002	1.46 (0.81, 2.63)	0.2
73-84	2.83 (1.49, 5.37)	0.001	1.92 (1.00, 3.66)	0.049
85 or more	6.44 (3.19, 13.01)	<0.001	2.61 (1.37, 4.95)	0.003

[1]Number of observations=912 (110 patients excluded from model due to missing data) and number of outlets=77. Covariates are those presented in Table.
[2]Patient completed all doses, verified by pill count when available. Data missing for 5 patients.
[3]For each dose, patients took the correct number of pills at the correct time of day, verified by pill count when available. Data missing for 23 patients.
[4]Age categories based on recommended age breakdown for AL blister packs in Tanzania.
[5]Wealth quintiles pooled for public health facilities and ADDOs using principal component analysis of sampled patients based on standard Demographic and Health Survey variables.

Table 4 Multivariate analyses of factors associated with adherence by sector

	Verified completed treatment[1]				**Verified timely completion[2]**			
	Public health facilities (N=572)[3]		ADDOs (N=450)[4]		Public health facilities (N=572)[3]		ADDOs (N=450)[4]	
	Adjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Age[5]								
Under 3 years (ref)	---	---	---	---	---	---	---	---
3 years to under 8 years	1.32 (0.76, 2.28)	0.3	0.69 (0.35, 1.36)	0.3	1.03 (0.60, 1.78)	0.9	0.51 (0.28, 0.93)	0.029
8 years to under 12 years	1.33 (0.49, 3.57)	0.6	0.97 (0.43, 2.16)	0.9	2.25 (0.74, 6.86)	0.2	0.75 (0.31, 1.82)	0.5
12 years and above	1.19 (0.62, 2.31)	0.6	0.94 (0.48, 1.84)	0.9	1.06 (0.59, 1.93)	0.8	0.69 (0.35, 1.38)	0.3
Patient (or caregiver if patient below age 12) completed primary school	1.16 (0.70, 1.91)	0.6	1.56 (1.00, 2.43)	0.050	0.88 (0.55, 1.40)	0.6	0.94 (0.54, 1.63)	0.8
Socio-economic status[6]								
1st quintile (most poor, ref)	---	---	---	---	---	---	---	---
2nd quintile	0.97 (0.60, 1.57)	0.9	0.82 (0.38, 1.81)	0.6	0.93 (0.52, 1.64)	0.8	1.19 (0.62, 2.26)	0.6
3rd quintile	1.04 (0.54, 1.98)	0.9	1.48 (0.72, 3.03)	0.3	0.70 (0.37, 1.34)	0.3	2.84 (1.15, 7.05)	0.024
4th quintile	2.20 (1.09, 4.47)	0.038	1.75 (0.87, 3.51)	0.1	1.25 (0.64, 2.44)	0.5	1.82 (0.61, 5.45)	0.3
5th quintile (least poor)	2.19 (0.81, 5.93)	0.2	1.99 (0.71, 5.54)	0.2	2.21 (1.01, 4.82)	0.046	2.47 (0.93, 6.55)	0.070
Slept under a bed net the night before the interview	1.60 (1.10, 2.34)	0.015	0.98 (0.59, 1.62)	0.9	1.23 (0.77, 1.96)	0.4	0.79 (0.50, 1.27)	0.3
Sought care within two days of fever onset	1.01 (0.60, 1.72)	0.9	1.16 (0.63, 2.13)	0.6	1.61 (0.99, 2.61)	0.056	1.11 (0.59, 2.09)	0.8
Fever symptoms	3.38 (1.21, 9.47)	0.020	1.18 (0.56, 2.47)	0.7	1.65 (0.64, 4.25)	0.3	0.86 (0.47, 1.58)	0.6
Distance from home to outlet within 2.5 km[7]	1.67 (1.05, 2.65)	0.031	0.76 (0.48, 1.20)	0.2	1.14 (0.68, 1.91)	0.6	1.09 (0.65, 1.82)	0.8
Time of day drug was obtained								
Morning (ref)	---	---	---	---	---	---	---	---
Afternoon	1.11 (0.62, 2.01)	0.7	1.12 (0.52, 2.38)	0.8	0.55 (0.31, 0.97)	0.038	1.04 (0.57, 1.88)	0.9
Evening	0.81 (0.22, 3.04)	0.7	0.95 (0.44, 2.05)	0.9	0.10 (0.02, 47.6)	0.004	0.69 (0.31, 1.53)	0.4
Time between obtaining AL and interview (hours)								
60-67 (ref)	---	---	---	---	---	---	---	---
68-72	2.37 (0.87, 6.51)	0.093	2.80 (1.35, 5.82)	0.006	1.47 (0.44, 4.95)	0.5	1.55 (0.71, 3.36)	0.3
73-84	3.64 (1.31, 10.08)	0.013	2.73 (1.12, 6.63)	0.027	2.03 (0.56, 7.29)	0.3	2.94 (1.20, 7.20)	0.018

85 or more	5.59 (1.66, 18.79)	0.005	5.94 (2.70, 13.06)	<0.001	2.72 (0.75, 9.84)	0.1	2.09 (0.85, 5.13)	0.1
Tested for malaria at outlet	1.30 (0.82, 2.04)	0.3	0.39 (0.17, 0.85)	0.018	1.47 (0.96, 2.26)	0.078	0.48 (0.24, 0.97)	0.041
Took first dose of AL at outlet	1.05 (0.71, 1.55)	0.8	1.34 (0.60, 3.01)	0.5	2.11 (1.46, 3.04)	<0.001	1.33 (0.57, 3.13)	0.5
Recalled correct instructions given by dispenser on the number of pills per dose, number of doses, and number of days to take AL	4.04 (2.59, 6.31)	<0.001	2.98 (2.03, 4.37)	<0.001	6.09 (3.71, 10.02)	<0.001	2.51 (1.41, 4.45)	0.002
Recalled that dispenser used packaging as a visual aid to explain how to take AL	1.33 (0.75, 2.36)	0.3	1.28 (0.62, 2.66)	0.5	1.85 (1.09, 3.11)	0.022	1.40 (0.73, 2.67)	0.3
Reported being told to take the second dose of AL eight hours after the first dose	1.15 (0.74, 1.79)	0.5	1.28 (0.87, 1.89)	0.2	0.85 (0.52, 1.38)	0.5	1.77 (1.12, 2.80)	0.015
Reported being told to complete all doses of AL even if feeling better	0.96 (0.54, 1.71)	0.9	1.02 (0.61, 1.70)	0.9	0.44 (0.28, 0.70)	0.001	1.05 (0.73, 1.50)	0.8

[1]Patient completed all doses, verified by pill count when available. Data missing for 2 public health facility patients and 3 ADDO patients.
[2]Patient completed each dose at correct time with the correct number of pills per dose, verified by pill count when available. Data missing for 13 public health facility patients and 10 ADDO patients.
[3]Standard errors adjusted for 37 clusters.
[4]Standard errors adjusted for 40 clusters.
[5]Age categories based on recommended age breakdown for AL blister packs in Tanzania.
[6]Wealth quintiles pooled for public health facilities and ADDOs using principal component analysis of sampled patients based on standard Demographic and Health Survey variables.
[7]Based on GPS coordinates. Data missing from 30 public health facility patients and 52 ADDO patients.

Additional file 1 Association of patient characteristics with adherence by sector

	Verified completed treatment[1]						**Verified timely completion[2]**					
	Public health facilities (N=572)			Private ADDOs (N=450)			Public health facilities (N=572)			Private ADDOs (N=450)		
	Percent adherent	Unadjusted odds ratio (95% CI)	p-value	Percent adherent	Unadjusted odds ratio (95% CI)	p value	Percent adherent	Unadjusted odds ratio (95% CI)	p-value	Percent adherent	Unadjusted odds ratio (95% CI)	p-value
Sex												
Female (ref)	73.5	---	---	66.0	---	---	46.7	---	---	33.3	---	---
Male	75.9	1.13 (0.74, 1.74)	0.5	73.1	1.40 (0.88, 2.21)	0.2	45.0	0.93 (0.70, 1.25)	0.7	36.0	1.13 (0.81, 1.57)	0.5
Age[3]												
Under 3 years (ref)	72.8	---	---	70.4	---	---	46.5	---	---	38.8	---	---
3 years to under 8 years	76.3	1.20 (0.78, 1.84)	0.4	66.7	0.84 (0.46, 1.54)	0.6	45.9	0.98 (0.63, 1.51)	0.9	29.4	0.66 (0.40, 1.08)	0.095
8 years to under 12 years	75.7	1.16 (0.54, 2.51)	0.7	73.2	1.15 (0.52, 2.56)	0.7	48.7	1.09 (0.63, 1.90)	0.8	39.0	1.01 (0.50, 2.04)	0.9
12 years and above	75.4	1.14 (0.63, 2.06)	0.7	70.4	1.00 (0.58, 1.72)	0.9	44.3	0.92 (0.59, 1.43)	0.7	35.0	0.85 (0.53, 1.37)	0.5
Patient (or caregiver if patient below age 12) completed primary school[4]												
No (ref)	70.8	---	---	59.1	---	---	45.9	---	---	30.7	---	---
Yes	77.8	1.45 (1.03, 2.04)	0.033	74.1	1.98 (1.27, 3.11)	0.003	46.4	1.02 (0.75, 1.39)	0.9	36.4	1.30 (0.84, 1.99)	0.2
Socioeconomic status[5]												
1st quintile (most poor, ref)	69.2	---	---	63.0	---	---	42.0	---	---	29.6	---	---
2nd quintile	70.5	1.06 (0.69, 1.64)	0.8	57.1	0.78 (0.40, 1.55)	0.5	44.5	1.11 (0.68, 1.81)	0.7	25.8	0.83 (0.45, 1.53)	0.6
3rd quintile	71.7	1.13 (0.67, 1.90)	0.7	67.0	1.19 (0.72, 1.99)	0.5	38.2	0.85 (0.51, 1.41)	0.5	39.6	1.56 (0.69, 3.53)	0.3
4th quintile	85.9	2.70 (1.54, 4.74)	0.001	73.8	1.65 (0.85, 3.20)	0.1	53.1	1.56 (0.91, 2.68)	0.1	35.6	1.32 (0.57, 3.07)	0.5
5th quintile (least poor)	86.4	2.84 (1.21, 6.67)	0.017	76.4	1.90 (0.92, 3.93)	0.085	64.3	2.48 (1.36, 4.52)	0.003	36.6	1.38 (0.62, 3.05)	0.4
Slept under a bed net the night before the interview												
No (ref)	68.2	---	---	70.3	---	---	42.6	---	---	41.7	---	---

Yes	76.9	1.55 (1.16, 2.07)	0.003	69.5	0.96 (0.63, 1.47)	0.9	47.2	1.21 (0.81, 1.80)	0.4	31.7	0.65 (0.45, 0.94)	0.021
Sought care prior to attending the study outlet												
No (ref)	74.4	---	---	68.8	---	---	46.6	---	---	32.6	---	---
Yes	75.2	1.05 0.73, 1.51)	0.8	71.4	1.13 (0.71, 1.81)	0.6	45.1	0.94 (0.66, 1.34)	0.7	38.4	1.29 (0.87, 1.91)	0.2
Sought care within two days of fever onset[6]												
No (ref)	71.0	---	---	66.9	---	---	36.2	---	---	32.3	---	---
Yes	75.6	1.27 (0.84, 1.91)	0.3	71.0	1.21 (0.75, 1.92)	0.4	48.8	1.68 (1.15, 2.46)	0.008	35.8	1.17 (0.76, 1.79)	0.5
Fever symptoms												
No (ref)	58.8	---	---	65.0	---	---	39.4	---	---	35.0	---	---
Yes	75.6	2.16 (1.09, 4.31)	0.028	70.3	1.27 (0.64, 2.55)	0.5	46.4	1.33 (0.65, 2.72)	0.4	34.8	0.99 (0.54, 1.80)	0.9
Respiratory symptoms												
No (ref)	74.9	---	---	69.7	---	---	46.6	---	---	34.2	---	---
Yes	72.5	0.88 (0.53, 1.47)	0.6	70.6	1.04 (0.47, 2.30)	0.9	42.3	0.84 (0.59, 1.21)	0.4	41.2	1.35 (0.65, 2.78)	0.4
Stomach ache												
No (ref)	71.3	---	---	69.0	---	---	44.4	---	---	33.3	---	---
Yes	77.4	1.38 (0.96, 1.97)	0.082	70.6	1.08 (0.78, 1.49)	0.6	47.3	1.13 (0.86, 1.48)	0.4	36.2	1.14 (0.79, 1.63)	0.5
Fatigue												
No (ref)	75.2	---	---	69.4	---	---	46.3	---	---	34.0	---	---
Yes	69.0	0.73 (0.45, 1.21)	0.2	71.6	1.11 (0.64, 1.93)	0.7	42.9	0.87 (0.46, 1.63)	0.7	38.3	1.20 (0.71, 2.05)	0.5
Joint / body pain												
No (ref)	74.7	---	---	70.0	---	---	45.7	---	---	33.1	---	---
Yes	73.9	0.96 (0.56, 1.65)	0.9	69.3	0.97 (0.65, 1.46)	0.9	47.6	1.08 (0.71, 1.66)	0.7	38.5	1.27 (0.80, 1.99)	0.3
Convulsions												
No (ref)	74.3	---	---	69.7	---	---	46.4	---	---	34.5	---	---
Yes	85.7	2.08 (0.44, 9.74)	0.4	100[7]	---	---	28.6	0.46 (0.16, 1.34)	---	100[7]	---	---
Other symptoms[8]												
No (ref)	74.4	---	---	70.4	---	---	45.1	---	---	34.4		
Yes	75.7	1.07 (0.63, 1.83)	0.8	64.4	0.76 (0.41, 1.40)	0.4	52.2	1.33 (0.75, 2.35)	0.3	38.6	1.20 (0.57, 2.55)	0.6

Outlet ward												
Rural (ref)	76.2	---	---	68.8	---	---	46.1	---	---	36.3	---	---
Urban	64.0	0.56 (0.26, 1.18)	0.1	70.3	1.07 (0.63, 1.81)	0.8	45.3	0.97 (0.51, 1.85)	0.9	34.1	0.91 (0.52, 1.59)	0.7
Distance from home to outlet by GPS coordinates[9]												
More than 2.5 km (ref)	66.3	---	---	71.9	---	---	42.3	---	---	33.3	---	---
2.5 km or less	78.1	1.81 (1.20, 2.75)	0.005	65.8	0.75 (0.54, 1.06)	0.1	48.1	1.26 (0.83, 1.92)	0.3	33.8	1.02 (0.70, 1.50)	0.9
Time of day drug was obtained												
Morning (ref)	75.7	---	---	75.5	---	---	49.9	---	---	43.1	---	---
Afternoon	73.3	0.88 (0.50, 1.54)	0.7	67.5	0.67 (0.40, 1.15)	0.2	38.5	0.63 (0.43, 0.92)	0.017	34.2	0.69 (0.41, 1.16)	0.2
Evening	58.3	0.45 (0.22, 0.93)	0.031	63.0	0.55 (0.35, 0.89)	0.014	8.3	0.09 (0.02, 0.37)	0.001	22.4	0.38 (0.18, 0.79)	0.010
Time between obtaining AL and interview (hours)[10]												
60-67	53.1	---		54.5	---	---	18.9			19.3	---	---
68-72	72.0	2.27 (1.20, 4.00)	0.004	72.1	2.16 (1.25, 3.71)	0.006	43.3	3.31 (1.42, 7.70)	0.005	35.6	2.31 (1.19, 4.50)	0.013
73-84	76.8	2.92 (1.47, 5.82)	0.002	70.5	1.99 (1.08, 3.69)	0.028	47.8	3.96 (1.70, 9.20)	0.001	43.5	3.22 (1.62, 6.42)	0.001
85 or more	84.0	4.62 (2.00, 10.63)	<0.001	87.3	5.74 (3.14, 10.49)	<0.001	56.3	5.57 (2.26, 13.75)	<0.001	44.3	3.33 (1.66, 6.69)	0001

[1]Patient completed all doses, verified by pill count when available. Data missing for 2 public health facility patients and 3 ADDO patients.
[2]Patient completed each dose at correct time with the correct number of pills per dose, verified by pill count when available. Data missing for 13 public health facility patients and 10 ADDO patients.
[3]Age categories based on recommended age breakdown for AL blister packs in Tanzania.
[4]Caregiver education missing for five patients attending public health facilities.
[5]Wealth quintiles pooled for public health facility and ADDO clients using principal component analysis of sampled patients based on standard Demographic and Health Survey variables. Data missing for public health facility patient.
[6]Number of days since illness onset missing for 3 public health facility patients and 11 ADDO patients.
[7]Analysis not possible as only 2 ADDO patients reported convulsions.
[8]Includes dizziness, crying/fussiness, startling (kustukastuka), sleep-talking (kuweweseka), worms, fast heart rate, stays in sun, red/inflamed eyes, and sores/ulcers.
[9]GPS data missing from 30 public health facility patients and 52 ADDO patients.
[10]Rounded to nearest hour. Data missing for 15 public health facility patients and 6 ADDO patients.

Additional file 2 Association of factors related to care received at outlet and patient status at interview with adherence by sector

	Verified completed treatment[1]						**Verified timely completion[2]**					
	Percent adherent, Public health facilities (N=572)	Unadjusted odds ratio (95% CI)	p-value	Percent adherent, ADDOs (N=450)	Unadjusted odds ratio (95% CI)	p value	Percent adherent, Public health facilities (N=572)	Unadjusted odds ratio (95% CI)	p-value	Percent adherent, ADDOs (N=450)	Unadjusted odds ratio (95% CI)	p-value
Tested for malaria at outlet												
No (ref)	70.0	---	---	70.7	---	---	40.1	---	---	35.5	---	---
Yes	78.8	1.59 (1.09, 2.33)	0.016	62.0	0.68 (0.31, 1.46)	0.3	50.8	1.55 (1.12, 2.13)	0.008	30.0	0.78 (0.41, 1.50)	0.5
Told diagnosis at outlet												
No (ref)	71.3	---	---	68.3	---	---	45.7	---	---	35.3	---	---
Yes	77.4	1.38 (0.83, 2.28)	0.2	71.8	1.18 (0.76, 1.84)	0.5	46.3	1.02 (0.68, 1.54)	0.9	34.4	0.96 (0.70, 1.30)	0.8
Took first dose of AL at outlet												
No (ref)	73.8	---	---	68.8	---	---	40.2	---	---	34.0	---	---
Yes	75.8	1.11 (0.73, 1.70)	0.6	79.1	1.71 (0.87, 3.39)	0.1	54.4	1.78 (1.29, 2.45)	<0.001	41.9	1.40 (0.67, 2.90)	0.4
Obtained correct blister pack for age[3]												
No (ref)	78.3	---	---	65.8	---	---	47.8	---	---	34.2	---	---
Yes	73.6	0.77 (0.45, 1.30)	0.3	70.6	1.25 (0.86, 1.83)	0.3	45.5	0.91 (0.61, 1.36)	0.7	34.9	1.03 (0.59, 1.79)	0.9
Paid for AL												
No (ref)	75.1	---	---	69.6	---	---	47.8	---	---	30.0	---	---
Yes	73.6	0.92 (0.59, 1.44)	0.7	80.0	0.57 (0.14, 2.35)	0.4	41.8	0.79 (0.55, 1.12)	0.2	34.9	1.25 (0.29, 5.42)	0.8
Recalled correct instructions given by dispenser on the number of pills per dose, number of doses, and number of days to take AL												
No (ref)	58.3	---	---	55.6	---	---	22.8	---	---	22.4	---	---
Yes	85.0	4.06 (2.71, 6.09)	<0.001	79.4	3.08 (2.16, 4.41)	<0.001	60.9	5.26 (3.59, 7.71)	<0.001	43.3	2.65 (1.68, 4.19)	<0.001
Recalled that												

dispenser used packaging as a visual aid to explain how to take AL												
No (ref)	65.4	---	---	61.6	---	---	32.1	---	---	26.0	---	---
Yes	76.3	1.70 (1.04, 2.78)	0.036	71.4	1.56 (0.94, 2.59)	0.090	48.3	1.98 (1.29, 3.05)	0.002	36.5	1.64 (1.01, 2.65)	0.046
Reported being told to take the second dose of AL eight hours after the first dose												
No (ref)	67.4	---	---	59.8	---	---	41.7	---	---	24.8	---	---
Yes	79.8	1.91 (1.30, 2.80)	0.001	75.6	2.09 (1.56, 2.80)	<0.001	49.1	1.35 (0.94, 1.92)	0.1	40.5	2.06 (1.44, 2.94)	<0.001
Reported being told to take AL with food or milk												
No (ref)	72.5	---	---	66.1	---	---	45.8	---	---	33.7	---	---
Yes	75.8	1.19 (0.72, 1.96)	0.5	72.1	1.33 (0.91, 1.93)	0.1	46.1	1.01 (0.65, 1.56)	0.9	35.4	1.08 (0.69, 1.68)	0.7
Reported being told to complete all doses of AL even if feeling better												
No (ref)	66.7	---	---	63.2	---	---	46.0	---	---	28.1	---	---
Yes	76.9	1.67 (1.09, 2.56)	0.019	73.6	1.62 (1.13, 2.34)	0.009	46.1	1.00 (0.65, 1.55)	0.9	38.6	1.61 (1.25, 2.06)	<0.001
Reported being told to take a replacement dose in case of vomiting within half hour of taking a dose												
No (ref)	74.4	---	---	69.8	---	---	46.1	---	---	35.0	---	---
Yes	81.8	1.55 (0.37, 6.40)	0.6	72.7	1.16 (0.40, 3.36)	0.8	40.0	0.78 (0.19, 3.21)	0.7	27.3	0.70 (0.19, 2.59)	0.6
Reported being told about possible side effects												
No (ref)	74.7	---	---	70.1	---	---	45.7	---	---	35.1	---	---
Yes	76.9	1.13 (0.32, 4.03)	0.9	76.9	1.42 (0.37, 5.39)	0.6	61.5	1.90 (0.72, 5.06)	0.2	30.8	0.82 (0.25, 2.75)	0.8
Reported current												

fever at time of interview												
No (ref)	75.2	---	---	72.1	---	---	46.7	---	---	35.7	---	---
Yes	71.8	0.84 (0.53, 1.34)	0.5	56.3	0.50 (0.27, 0.94)	0.031	42.1	0.83 (0.55, 1.26)	0.4	29.2	0.74 (0.40, 1.37)	0.3
Could play or work at time of interview												
No (ref)	64.3	---	---	39.4	---	---	43.9	---	---	23.5	---	---
Yes	75.5	1.71 (0.85, 3.44)	0.1	72.4	4.04 (1.88, 8.66)	<0.001	46.1	1.09 (0.58, 2.05)	0.8	35.8	1.81 (0.74, 4.42)	0.2
Tested positive by mRDT at interview[4]												
No (ref)	76.1	---	---	69.8	---	---	47.5	---	---	36.6	---	---
Yes	73.7	0.88 (0.51, 1.51)	0.6	69.8	1.00 (0.69, 1.45)	0.9	44.9	0.90 (0.57, 1.41)	0.6	33.3	0.87 (0.60, 1.25)	0.4
Tested positive by blood smear collected at interview[5]												
No (ref)	74.6	---	---	69.8	---	---	45.3	---	---	35.6	---	---
Yes	75.0	1.02 (0.35, 2.98)	0.9	66.7	0.87 (0.15, 4.88)	0.9	56.3	1.56 (0.60, 4.04)	0.4	33.3	0.91 (0.15, 5.60)	0.9

[1]Patient completed all doses, verified by pill count when available. Data missing for 2 public health facility patients and 3 ADDO patients.
[2]Patient completed each dose at correct time with the correct number of pills per dose, verified by pill count when available. Data missing for 13 public health facility patients and 10 ADDO patients.
[3]Age categories based on recommended age breakdown for AL blister packs in Tanzania.
[4]RDT data missing for 7 public health facility patients and 17 ADDO patients.
[5]Blood smear data missing for 15 public health facility patients and 18 ADDO patients.

6.3 Supplementary data

This section presents two additional analyses. First, Table 6.3.1 shows the percentage of patients taking AL with fatty food and the percentage vomiting within half an hour of taking a dose. Secondly, Tables 6.3.2 and 6.3.3 show the concordance of RDT and blood smear results in public health facility and ADDO patients, respectively.

Food intake and vomiting. Taking AL with fatty food is important for optimal lumefantrine absorption [1]. One study demonstrated a 16-fold variation in lumefantrine bioavailability among healthy Thai adults compared to volunteers that had not taken a fatty meal [2]. Another study showed that a small amount of fat was necessary for lumefantrine absorption, but only 1.2 g, the amount in 36 ml of soya milk, was sufficient [3].

In Tanzania, national guidelines state that each dose of AL should be taken with meals [4], but whether or not the meal must contain fat is less clear [5]. Foods commonly eaten in Tanzania that contain fat are cow milk or breast milk, oil used in cooking, coconuts, peanuts, cashews, avocados, eggs, fish, and meat, although people of lower socioeconomic status may not be able to afford some of these foods. Relatively inexpensive foods such as porridge (*uji* or *ugali*), cassava, maize, and fruits have little fat on their own. Guidelines also state that the first dose should be taken under observation of the dispenser, although many patients have not brought food to the outlet and cannot afford to purchase food from vendors [5]. Furthermore, if a dose is vomited, a replacement dose must be obtained, but guidelines do not specify how replacements should be obtained.

Table 6.3.1 shows that the majority of patients in the studies presented in the research paper in this chapter took at least one dose with a meal, although this was slightly higher for public health facility patients compared to ADDO patients (94% vs. 89%, p=0.023). Approximately 70% of patients attending both sectors took at least one dose with fatty food, and 10% of patients reported vomiting at least one dose. Very few of these patients (14/108) reported obtaining replacement doses.

Among patients who completed treatment, 38% of public health facility patients and 37% of ADDO patients took all six doses with food, and very few patients took all six doses with fatty food (7% and 10%, respectively), with no difference between sector.

Table 6.3.1 Patient report of taking AL with food and occurrence of vomiting (%, 95% CI)[1]

	Public health facilities (N=572 patients from 40 outlets)	Private ADDOs (N=450 patients from 37 outlets)	p-value
Took at least one dose with food or drink	94.2 (91.5, 96.0)	89.0 (83.7, 92.7)	0.023
Took at least one dose with fatty food or milk	72.0 (66.8, 76.6)	69.7 (63.2, 75.5)	0.5
Vomited within 30 minutes after at least one dose[2]	10.7 (7.9, 14.3)	10.5 (8.0, 13.6)	0.9
Of those who completed treatment:			
Took all six doses with food or drink	37.9 (31.8, 44.3)	36.7 (30.3, 43.6)	0.7
Took all six doses with fatty food or milk	6.9 (4.6, 10.2)	9.7 (6.5, 14.3)	0.2
Did not vomit after any dose	90.1 (85.7, 93.3)	90.3 (86.3, 93.2)	0.9

[1]Data missing for 10 patients for taking at least one dose with food / fatty food; for 3 patients on vomiting after at least one dose; for 9 patients who completed treatment on taking all doses with food / fatty food; and for 3 patients who completed treatment on vomiting after any dose.
[2]Only 6 public health facility patients and 8 ADDO patients took a replacement dose after vomiting.

These results show that a low proportion of patients reported taking all six doses with any food or drink, and very few patients reported taking all six doses with fatty food. In contrast, 60% of patients reported being told to take AL with food or milk. No differences were observed between sector in taking all doses with food or fatty food, or in reported advice. Other studies in public health facilities in Tanzania have also found very low proportions of patients taking AL with food [5-7]. Possible reasons for this include a lack of understanding among patients that the drug should be taken with food, difficulty eating when ill, or not having food available. In the study presented in the research paper, several patients (n=10) reported not having food available as a reason for stopping treatment. While infrequent,

this resonates with anecdotal accounts from dispensers that telling patients to take AL with food, and particularly fatty food, could result in confusion that discourages adherence. There is also potential for confusion with instructions for DHA-piperaquine, which should not be taken within three hours before or after eating due to the risk for prolongation of the corrected electrocardiograph (QT) interval [8].

Approximately 10% of patients vomited at least one dose, with very few patients obtaining a replacement dose. However, 72 of the 108 patients who reported vomiting were considered to have completed treatment, although only five of these had obtained a replacement dose. This may have resulted in slightly overestimated adherence in both sectors.

In the data presented in the research paper, only about 2% of both public health facility and ADDO patients reported being told to obtain a replacement dose in case of vomiting within half an hour of taking a dose. Dispensers might be concerned that telling patients about vomiting or minor side effects would affect their adherence or, in ADDOs, discourage them from purchasing the drug. They might also be unsure of how patients who vomit should obtain a replacement dose, as AL is only available in blister packs that are not intended to be split. Another study in Tanzania reported that half of all caretakers thought a replacement dose could be taken from the existing blister pack [7]. There is thus a need to clarify guidelines and options for patients who require replacement doses.

RDT and blood smear data concordance. As shown in the research paper in this chapter, 50% of public health facility patients and 28% of ADDO patients were positive by RDT at the interview on day 4, while only 3% and 1.4%, respectively, were positive by reference blood smear. Tables 6.3.2 and 6.3.3 show the matrices of RDT and blood smear concordance in public health facilities and ADDOs. Among patients testing positive by RDT, 5.4% of public health facility and 3.3% of ADDO patients had a positive blood smear. Due to small numbers, it was not possible to look at the effect of adherence on RDT and blood smear concordance in each sector. However, among patients testing positive by RDT in both

sectors combined, there was no difference in the proportion of patients who did or did not complete treatment with a positive blood smear (4.6% and 5.5%, respectively, p=0.6).

Table 6.3.2 Matrix of RDT and blood smear results for public health facility patients[1]

	Blood smear positive	Blood smear negative	Total
RDT positive	15 (5.4%)	261 (94.6%)	276 (100%)
RDT negative	1 (0.4%)	279 (99.6%)	280 (100%)
Total	16 (2.9%)	540 (97.1%)	556 (100%)

[1]Data missing for 15 patients.

Table 6.3.3 Matrix of RDT and blood smear results for ADDO patients[1]

	Blood smear positive	Blood smear negative	Total
RDT positive	4 (3.3%)	117 (96.7%)	121 (100%)
RDT negative	2 (0.6%)	309 (99.4%)	311 (100%)
Total	6 (1.4%)	426 (98.6%)	432 (100%)

[1]Data missing for 18 patients.

In order to measure effectiveness of AL, a longer follow up period (e.g. 28 or optimally 42 days) would be required. Although the artemether component of AL is rapidly absorbed and effectively clears parasites, the lumefantrine component has a longer elimination half-life and acts to prevent recrudescence [9, 10]. Thus, sub-microscopic parasites not exposed to sufficient lumefantrine, due to metabolic factors or not taking all doses, could survive and ultimately cause treatment failure. In the studies presented in this chapter, the small number of patients with positive blood smears might have made it difficult to detect any differences in patient adherence. However, even studies with 28 or 42-day follow up periods have seen very high effectiveness and have thus been unable to tease out the effects of adherence [11-13]. These challenges are discussed further in Chapter 8.

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7 Methods of measuring adherence

7.1 Introduction

Chapters 5 and 6 have reported adherence measures based on self-report and pill count, as is common in the literature. However, there are concerns that self-reported data are not accurate due to patient recall and social desirability biases. In this chapter, we describe an assessment of the validity of self-report verified by pill count, using the novel approach of smart blister packs.

7.2 Research paper (cover sheet on next page)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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SECTION A – Student Details

Student	Katia Bruxvoort
Principal Supervisor	David Schellenberg
Thesis Title	Evaluating patient adherence to artemether-lumefantrine obtained from public and private drug outlets in Tanzania

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
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Where is the work intended to be published?	PLOS ONE
Please list the paper's authors in the intended authorship order:	Katia Bruxvoort, Charles Festo, Matthew Cairns, Admirabilis Kalolella, Frank Mayaya, S. Patrick Kachur, David Schellenberg and Catherine Goodman
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had the primary role of designing the study, overseeing field work, analysing the data, and drafting the manuscript.

Student Signature: Katya Bunnant Date: 14 Dec 2014

Supervisor Signature: DS Date: 15 Dec 14

Measuring patient adherence to malaria treatment: A comparison of results from self-report and a customised electronic monitoring device

Katia Bruxvoort[1,2], Charles Festo[2], Matthew Cairns[1], Admirabilis Kalolella[2], Frank Mayaya[2], S. Patrick Kachur[3], David Schellenberg[1] and Catherine Goodman[1]

[1]*London School of Hygiene and Tropical Medicine, London, UK*

[2]*Ifakara Health Institute, Dar es Salaam, Tanzania*

[3]*U.S. Centers for Disease Control and Prevention, Atlanta, USA*

Corresponding author: Katia Bruxvoort, katia.bruxvoort@lshtm.ac.uk

Abstract

Self-report is the most common and feasible method for assessing patient adherence to medication, but can be prone to recall bias and social desirability bias. Most studies assessing adherence to artemisinin-based combination therapies (ACTs) have relied on self-report. In this study, we use a novel customised electronic monitoring device — termed smart blister packs — to examine the validity of self-reported adherence to artemether-lumefantrine (AL) in southern Tanzania.

Smart blister packs were designed to look identical to locally available AL blister packs and to record the date and time each tablet was removed from packaging. Patients obtaining AL at randomly selected health facilities and drug stores were followed up at home three days later and interviewed about each dose of AL taken. Blister packs were requested for pill count and extraction of smart blister pack data.

Data on adherence from both self-report verified by pill count and smart blister packs were available for 696 of 1,204 patients. There was no difference between methods in the proportion of patients assessed to have completed treatment (64% and 67%, respectively). However, the percentage taking the correct number of pills for each dose at the correct times (timely completion) was higher by self-report than smart blister packs (37% vs. 24%; $p<0.0001$). By smart blister packs, 64% of patients completing treatment did not take the correct number of pills per dose or did not take each dose at the correct time interval.

Smart blister packs resulted in lower estimates of timely completion of AL and may be less prone to recall and social desirability bias. They may be useful when data on patterns of adherence are desirable to evaluate treatment outcomes. Improved methods of collecting self-reported data are needed to minimise bias and maximise comparability between studies.

Keywords: Patient adherence, measuring adherence, self-report, electronic monitoring, ACTs

Introduction

Self-reported adherence, based on detailed questionnaires, is considered the most feasible method for assessing adherence in resource-poor settings [1,2]. Self-reported data are relatively low cost to collect and do not involve complicated field logistics or invasive procedures such as blood sampling. However, despite its many advantages, self-reported adherence is prone to several sources of bias [2-4]. Data may be subject to recall bias if patients do not accurately recall their treatment history, including the number of pills taken, day and time of each dose, and when the full course was completed. Social desirability bias may also occur if patients provide perceived expected responses in order to avoid being seen as negligent.

Several other methods have been used to complement or even replace patient recall. Many studies verify self-reported adherence by counting the number of pills remaining in packaging, although this is not always accurate as patients may remove pills without taking them, or packaging may not be available for inspection [5,6]. Electronic methods of assessing adherence have been used extensively in chronic diseases, mostly in the form of pill containers with caps that record the day and time the container is opened, such as MEMS™ [4,7]. While not feasible for routine clinical practice in many parts of the world, MEMS™ have been used to validate other adherence measures in studies of adherence to antimalarial drugs [8,9], tuberculosis treatment [10], and antiretroviral therapy [11].

Artemisinin-based combination therapies (ACTs) are first line treatment for malaria in most endemic countries and are increasingly obtained by patients seeking treatment in both public and private health sectors. Good patient adherence is required to maximise their clinical impact and minimise the rate of development of drug-resistance [12-14]. A number of studies assessing adherence to ACTs have been conducted in recent years, with results showing that anywhere between 39% and 100% of patients can be considered adherent [5,6], reflecting both genuine differences in adherence as well as variation in study design and measurement methods. The majority of these studies relied on self-report with or without pill count. One study in Malawi used MEMS™ containers and found 100% adherence to artemether-lumefantrine (AL) by self-report and lower adherence (92%) by MEMS™ [8]. However, ACTs are now typically dispensed in blister packs designed to improve adherence [15] and look considerably different than MEMS™ containers. This may result in over-estimated adherence, as patients using MEMS™ are likely to be aware that their adherence is being monitored and their experience is no longer comparable to that of patients receiving unit doses in their customary packaging.

In this study, set in southern Tanzania, the validity of self-reported patient adherence to AL was assessed using a novel customised electronic monitoring device — termed smart blister packs — that

looked identical to regular AL packs, but contained a device that registered the date and time each pill was removed from the pack. This is the first study to our knowledge to employ this technology under routine conditions to investigate adherence to antimalarial treatment.

Methods

Study setting. The study was conducted in Mtwara, a rural region in southeastern Tanzania with more than a third of the population in the lowest national wealth quintile [16]. Community prevalence of falciparum malaria parasitaemia among children 6-59 months of age in Mtwara was 17.4% in the 2011-2012 HIV/AIDS and Malaria Indicator Survey [17].

In Tanzania, AL was introduced in public health facilities for treatment of uncomplicated malaria in 2006. The recommended treatment regimen is six doses over 3 days, with 1-4 tablets (each containing 20 mg artemether / 120 mg lumefantrine) per dose depending on the patient's weight / age band. National guidelines state that the second dose should be taken eight hours after the first dose, followed by the remaining doses each morning and evening of the second and third days [18].

In Tanzania's private sector, more than two thirds of antimalarial drug sales occur in small drug stores [19], many of which have been upgraded to Accredited Drug Dispensing Outlets (ADDOs) through a process of training and accreditation. ADDOs are allowed to sell a limited number of prescription-only drugs, including some antibiotics and ACTs [20,21]. By 2011, all drug shops in Mtwara were officially required to have upgraded to ADDO status, but in practice some shops had not yet paid fees or received training and were tolerated as "prospective ADDOs" (in this paper the term ADDOs is used to include both accredited outlets and "prospective ADDOs").

This study was embedded in two parallel and contemporaneous studies of adherence to AL: a cluster randomised trial of a text message intervention targeted at ADDO dispensers to improve knowledge of advice to provide when dispensing AL, and an observational adherence study in public

health facilities. Details and results of these studies are presented separately [22,23]. Smart blister pack data were collected from a subset of patients in both studies for the analyses reported here.

Smart blister packs. Smart blister packs were prepared using Med-ic® blister package technology (Information Mediary Corporation, Ottawa, Canada). This comprises a fine wire, connected to a microchip, across each blister. When a tablet is pushed through the foil, the wire is disrupted, and the precise time this occurs is recorded on the chip. Wallet cards were designed for all four weight / age bands of AL (Coartem®) and looked identical to AL locally available in Tanzania, but with a slight thickness near the top centre illustrations due to the electronic tag and cell battery (Figure 1). Smart blister packs were assembled by research assistants at the Ifakara Health Institute by folding the wallet cards around blister packs of Coartem® purchased in Tanzania and sealing adhesively. At the beginning of the study, the blister packs were activated by scanning with a portable device developed by Information Mediary Corporation. Following treatment, collected blister packs were scanned to retrieve data.

Sample size and selection of study outlets. We aimed to provide smart blister packs to all 936 patients required for the cluster randomised trial in ADDOs [23] and all 448 patients required for the observational adherence study in public health facilities [22]. However, sample size calculations indicated that 600 patients receiving smart blister packs were sufficient, assuming conservatively that sensitivity and specificity of self-report was 50%, with a true adherence of 60%, a design effect due to correlation of responses within outlets of 2.5, and a precision of 10 percentage points [24]. A small number of patients per outlet was desired in order to reduce any potential bias caused by increasing community awareness of the study's objectives. Thus, 40 public health facilities (but not hospitals) were randomly selected from a list of all dispensaries and health centres in Mtwara, and 82 ADDOs meeting study inclusion criteria [23] were randomly selected from a census register of all ADDOs in Mtwara.

Study procedures. From September through November 2012, dispensers at selected public health facilities and ADDOs were visited by study supervisors and given a standard introduction about the study's objectives. Dispensers were provided with smart blister packs of AL to be dispensed in public health facilities to patients prescribed ACTs, and in ADDOs to patients indicating an intention to purchase treatment for malaria. In order to limit patients' awareness of our primary interest in assessing adherence, which could have led to a biased assessment, dispensers were not told that the blister packs provided were any different than the regular AL packs used locally. Dispensers were told we would visit at home some, but not all, patients obtaining treatment for fever and were asked to fill out a registration form for all fever patients, including a description of where patients lived. Study staff visited outlets every day to check and collect registration forms. The intention was to register 12 patients obtaining ACTs in one week per outlet, but it took 2-3 weeks to recruit this number in some outlets.

Eligible patients who obtained AL were identified from the registration forms and followed up three days later (day 4). Where written informed consent was given, patients / caregivers were asked about demographic and socioeconomic characteristics, treatment-seeking history, symptoms, detailed information about each dose of AL taken, and advice provided by the dispenser. The blister packs were requested for a pill count and extraction of timestamp data, following a brief explanation of the nature and purpose of the smart blister packs. Blood smears were collected to detect infection at the time of interview, and histidine-rich protein II (HRP-2)-based malaria rapid diagnostic tests (RDTs) (Pf-specific from ICT Diagnostics, Cape Town, South Africa) were conducted to indicate infection prior to treatment. Blood smears were stained in the field and transported to the Ifakara Health Institute laboratory where they were double-read by two microscopists blinded to results from each other and the RDT. Discrepant readings were resolved by a third microscopist.

Adherence definitions. Adherence was defined by both self-report and smart blister packs in two ways: verified completed treatment and verified timely completion [5]. Patients were considered to

have verified completed treatment (hereafter termed completed treatment) by self-report if they reported taking all pills by the time of the follow up visit, verified by counting zero pills remaining in packaging. Patients who reported completing treatment but had pills remaining were considered non-adherent, as were patients who reported not completing treatment but presented an empty blister pack. Where blister packs were not available, self-report alone determined if patients completed treatment. By smart blister pack, patients were considered to have completed treatment if a timestamp was recorded for each pill by the time of the follow up visit.

Verified timely completion (hereafter termed timely completion) was a more stringent definition and included a time component. For self-report, Swahili times of day were used: “alfajiri” (early morning, defined here as 4:00 am – 6:59 am), “asubuhi” (morning, 7:00 am – 11:59 am), “mchana” (afternoon, 12:00 pm – 3:59 pm), “jioni” (evening, 4:00 pm – 6:59 pm), “usiku” (night, 7:00 pm – 9:59 pm), and “usiku sana” (late night, 10:00 pm – 3:59 am). Patients were considered to have self-reported timely completion if they took the correct number of pills for each dose and took each dose at the correct Swahili time of day. The second dose was considered correct if taken at the Swahili times of day corresponding with 8 hours after the beginning or end of the time interval for the Swahili time of day when the first dose was taken. For example, if the first dose was taken in the morning (“asubuhi”), then the second dose could be taken in the afternoon (“mchana”), evening (“jioni”), or night (“usiku”) of the same day (i.e. between 3:00 pm and 7:59 pm). Remaining doses were considered correct if taken at the Swahili times of day corresponding with 12 hours after the beginning or end of the time interval for the Swahili time of day when the previous dose was taken. As with completed treatment, examination of packaging when available was used to verify adherence.

By smart blister pack, patients were considered to have timely completion if they took the correct number of pills for each dose, and took the second dose eight hours plus or minus four hours

after the first dose, followed by taking each of the remaining doses 12 hours plus or minus four hours after the previous dose.

For describing non-adherence, we distinguish between "intended doses" and "actual doses." "Intended dose" refers to the pills that are intended by the manufacturer to be taken together at one of six specified times and, in the AL used in this study, grouped together in the blister packaging. "Actual dose" refers to pills that were actually taken together. An actual dose might have included pills that were not grouped together, or a different number than specified for the intended dose. Pills that were administered at least 30 minutes apart from each other were considered different actual doses.

Data entry and analysis. All patient and dispenser interview data were collected using personal digital assistants, and data extracted from study forms (census, registration, and follow-up forms) were double entered into a Microsoft Access databases. Data were analysed in Stata 11.0 (Stata Corporation, College Station, USA). McNemar's analysis for paired data and conditional logistic regression were used to test the difference in completed treatment and timely completion between self-report and smart blister packs.

Ethics. All questionnaires, consent forms, and other study documents were translated into Swahili and piloted prior to use. Written informed consent was collected from dispensers prior to census, patient registration, and interview and from patients or their caregivers prior to interview. The study protocol was approved by the ethical review boards of Ifakara Health Institute and London School of Hygiene and Tropical Medicine. CDC advisors provided technical assistance in design and analysis but were not engaged in data collection and did not have access to personal identifiers.

Results

Interviews were conducted with 1,204 patients from 117 outlets (five ADDOs were closed or refused to participate). Blister packs were not available for collection from 257 patients (21%). Smart

blister packs that had been damaged or from which data were not extractable were collected from 251 patients (21%). In total, data were extracted from the blister packs of 696 patients (58%) (Figure 2). Due to infeasible dosing patterns or errors in smart blister pack technology, 55 patients were excluded from the analysis of timely completion, but not the analysis of completed treatment, since pills remained in their blister packs. For self-report, this applied to 18 patients who reported taking a subsequent dose before an earlier dose. For smart blister pack data, this applied to 10 patients with timestamps recorded before the treatment was dispensed or after the pack was collected, and 27 patients with a different number of pills observed by the study team at scanning than the number read by the software.

Table 1 shows characteristics of patients with and without availability of smart blister pack data (results comparing patient characteristics and adherence to AL across outlet types are presented elsewhere [21]). Based on the recommended age groups for AL blister packs in Tanzania, 27% of the 696 patients with smart blister pack data available were in the youngest age group (under three years), 24% were three years to under eight years, 6% were eight years to under 12 years, and 43% were 12 years and above. Fewer patients without smart blister pack data available were under three years (21%) and more were 12 years and older (50%). Taking the first dose at the outlet was reported by 23% of patients with smart blister pack data available and 17% without (p=0.0281), but all other characteristics were similar for patients with and without availability of smart blister pack data.

Comparison of adherence by self-report and smart blister pack data

Completed treatment. For patients with both types of data available, estimates of completed treatment were similar by smart blister packs (67%) and self-report (64%), with little difference in adherence by weight / age band of AL (Table 2). Considering smart blister packs as a gold standard, sensitivity and specificity of self-reported adherence were 96% and 100% respectively (Supporting Information Table 1). It was not possible to calculate an odds ratio because there were no instances

where patients who reported completing treatment did not complete treatment by smart blister pack data.

Among patients who did not present blister packs for collection, self-reported completed treatment was higher (87%) compared to both all patients who presented blister packs (66%; p<0.0001) and patients for whom smart blister pack data were available (64%; p<0.0001). Self-reported completed treatment was slightly lower among patients with smart blister pack data available (64%) than among patients presenting damaged smart blister packs from which data were not extractable (72%; p=0.050).

Timely completion. Timely completion was 37% by self-report and 24% by smart blister pack data (Table 3), much lower than completed treatment. The odds of timely completion by smart blister pack data were 0.36 times that of self-report (95% CI: 0.29, 0.43, p <0.0001). Sensitivity and specificity of self-reported timely completion were 74% and 74% respectively (Supporting Information Table 2). Although the number of patients ages eight to 12 years with a 3x6 pack was relatively small, this group appeared to have slightly higher timely completion, especially by smart blister pack data (Table 3), than patients taking other packs. Adult patients (with 4x6 packs) also appeared to have slightly higher timely completion than the two youngest age groups according to smart blister pack data, but not self-report.

Timely completion consisted of two aspects, taking the correct number of pills for each dose and taking all six doses at the correct time intervals. Of the 418 patients with data on timely completion available who reported having completed treatment (Table 3), 97% reported taking the correct number of pills for each of six actual doses. In contrast, according to smart blister pack data, only 67% of the 436 patients completing treatment appeared to have taken the correct number of pills for each of six actual doses, a finding more pronounced for younger children than older children and adults. Of patients who reported completing treatment, 58% reported taking all six doses at the correct time intervals, compared with 40% of those completing treatment based on smart blister pack data. Thus, by self-report, correct time intervals were the primary obstacle for timely completion among patients who had

completed treatment, but the smart blister pack data revealed problems both with the correct number of pills for each dose and the correct time intervals between doses.

Patterns of non-adherence

Figure 3 shows the number of actual doses taken, ranging from 0-6 by self-report and from 0-8 by smart blister pack data. Overall, the proportions reporting completion of each dose were similar, except that by self-report more people reported taking six doses. This may be because patients were asked only about each of the six intended doses. Only about 5% of patients took more than six actual doses according to smart blister pack data, including both patients who completed treatment and those who did not (Figure 3 and Table 4). For both self-report and smart blister pack data, the median numbers of actual doses taken by patients who did not complete treatment were 4 for the 1x6 and 2x6 packs and 5 for the 3x6 and 4x6 packs. By self-report and smart blister pack data, respectively, the median total numbers of pills taken for patients who did not complete treatment were 4 and 4.5 for the 1x6 pack, 8 (by both methods) for the 2x6 pack, 15 and 13.5 for the 3x6 pack, and 20 (by both methods) for the 4x6 pack (Table 4).

For the first actual dose, timely completion (based only on taking the correct number of pills for each dose, as timeliness of the first dose was not assessed) was 98% by self-report and 87% by smart blister pack data. Timely completion for the second actual dose decreased to 71% by both self-report and smart blister pack data (Figure 4). For the third dose onward, timely completion by self-report was clearly higher than for the second dose (above 80%), but this increase was not evident in the smart blister pack data. Cumulatively, timely completion after two actual doses was similar for self-report and smart blister pack data, reflecting a slightly larger drop in timely completion by self-report. From dose three onwards, timely completion declined more rapidly by smart blister pack data.

Discussion

This paper examines the validity of self-reported adherence in comparison with smart blister packs that recorded the day and time pills were removed from packaging. Timely completion (37% by self-report and 24% by smart blister packs) was much lower than completed treatment (64% by self-report and 67% by smart blister packs). No difference was observed between self-report and smart blister pack data for the percentage of patients completing treatment, but timely completion was lower when assessed using smart blister pack data (OR=0.36, 95% CI: 0.29, 0.42, p<0.0001). Smart blister pack data showed that, even among patients who completed treatment, 33% did not take the correct number of pills for all doses, and 60% did not take each dose at the correct time interval.

This study has several limitations. First, recovery of blister packs might have been higher had dispensers and patients been more aware of the aims of the study. However, to avoid artificially increasing adherence, we intentionally did not tell dispensers or patients that the objective of the study was to assess adherence. Secondly, dispensers did not always accurately record the time that drugs were dispensed, despite daily visits by the study team and attempts to clarify times that were unclear. We therefore concluded that the data were not sufficiently robust to assess the timeliness of the first dose.

For both self-report and smart blister pack data, we allowed a margin of error around the correct time intervals when assessing timely completion. Clocks are not commonly used in rural Mtwara, and Swahili times of day which each cover several hours were therefore used for self-reported timely completion. Recorded timestamps plus or minus four hours were used to define acceptable limits for smart blister pack data. Among patients with timely completion by both methods, Swahili times of day corresponded well with timestamps, so it is unlikely that the definitions of timely completion affected the difference between methods. However, more stringent definitions for both methods might have

resulted in lower levels of timely completion. Variability in adherence definitions has been frequently noted as a challenge for comparing adherence results across studies [5,6,25].

Self-report and smart blister pack data have various advantages and disadvantages for assessing patient adherence to ACTs. Self-reported adherence is collected through interviews, which are relatively inexpensive and are a widely accepted method of collecting data in many populations, including in southern Tanzania. Nonetheless, collecting accurate self-reported data can be challenging. Patients may have provided expected answers on the number of pills taken for each dose, or not remembered, and interviewers reported that patients often seemed confused about when and how each dose was taken. Some patients reporting taking more pills in total than the number in the blister pack, and some reported taking a subsequent dose before a previous dose. In this study, specific questions were asked about each of the six intended doses. However, patients may have taken pills grouped in a way that differed from the intended doses in the blister packs, and may therefore have taken more than six actual doses, as smart blister pack data indicated was the case. If any actual doses beyond the six intended are not captured by self-report interviews, this could underestimate the percentage completing treatment. In order to avoid some of these challenges, data collection tools need to be improved and evaluated, for example, including both open and closed-ended questions to identify actual doses taken [6].

As part of both the completed treatment and timely completion definitions, self-report was verified by counting pills remaining in packaging for the 83% of patients that presented blister packs. Very few patients (9/696) reported completing treatment but had pills remaining, similar to the high concordance between self-report alone and pill count described in a review of adherence to medication across diseases [3]. While this suggests that definitions incorporating pill counts may not differ from self-report alone, the patients who did not present blister packs reported higher completed treatment than those who did present blister packs (85% vs. 68%). This suggests that requesting blister packs may

reduce over-reporting of adherence, unless patients for whom blister packs were not available were more likely to have finished packs and disposed of them. Blister packs were requested at the end of the questionnaire, which means patients could have removed pills from the pack after completing the interview but prior to presenting the pack.

Compared to smart blister packs, self-report generally over-reported timely completion, consistent with most other studies of electronic monitoring of adherence across diseases [4]. However, 27% (42 /155) of patients who did not report timely completion were found to have timely completion by smart blister pack data (Supporting Information Table 1). This is likely due to patient confusion when reporting dose history, which was noted frequently by study staff, or possibly removing pills for later consumption. Studies of adherence to tuberculosis treatment and antiretroviral therapy have also documented that some patients non-adherent by self-report were adherent by electronic pill containers [10,11]. Our smart blister pack data revealed how some patients took pills in more than six actual doses, or removed a large number of pills at once, including removal of all pills remaining in the packaging on the date of the interview - possibly at the time of the interview.

The smart blister packs were easy to assemble, the software and portable scanner were straightforward to use, and the packs were designed to look identical to regular AL packs commonly available in Tanzania. However, they had a slight bulge at the top of the package for a small chip that stored data. Some patients noticed this and opened up the packaging to investigate, damaging the capacity to record and extract timestamps. Several patients were alarmed when the chip was discovered, requiring the study team to provide full explanations to participants and village leaders. Other blister packs were destroyed when children were allowed to play with them after completion of treatment, or when dropped in water or fires before, during, or after taking pills.

Although smart blister packs accurately recorded when pills were removed from the packaging, it was also possible for a timestamp to be recorded for a pill if pressure had been applied and a pill was

partially removed, even if the seal was not obviously broken. While it was evident when timestamps were recorded before the treatment was dispensed to the patient or after the pack was collected, this could also have occurred in the middle of treatment, which could have altered timely completion estimates, though this is not thought to have occurred frequently. In addition, for some patients, the number of pills observed by the study team at scanning did not correspond with the number read by the software. Future smart blister pack designs should be improved to reduce the chances that timestamps would be recorded when pills weren't completely removed and to reduce the bulge in the packaging so that patients are less likely to notice and tamper with the packaging.

Another approach to getting insights into adherence is through the measurement of drug levels in patients' blood during follow-up. In the case of ACTs, this has been approached by measuring the concentration of the non-artemisinin partner drug since the artemisinin component is absorbed and eliminated rapidly [26]. We collected blood spots on filter paper for the assessment of lumefantrine concentrations. However, analysis 19-24 months after collection found lumefantrine concentrations below the lower limit of quantification, reflecting the need for filter papers to be stored at appropriate temperatures and ideally analysed within 4-6 weeks post-collection [27].

Moreover, studies of adherence to AL have not found significant differences in blood lumefantrine concentrations between patients considered adherent and non-adherent by self-report [8,28-30]. Some studies have reported significant differences in lumefantrine concentrations (usually measured 7 days after initiation of treatment) between supervised versus non-supervised patients [31-33]. These and other studies have not reported differences in treatment failure based on cut-offs of 280 ng / ml [29,31-33] or 175 ng / ml [8], which have been previously found to predict recrudescence [12,26]. In addition, lumefantrine is known to have high inter-individual metabolic variation, with factors such as weight, age, pregnancy, and fat intake affecting absorption [34-36]. As a result, while biological

measures of lumefantrine concentration might provide some additional objective information about adherence, they can be difficult to obtain, process and interpret in follow-up studies.

Finally, methods for measuring adherence should be based on levels and components of adherence that are important for effectiveness. The recommended regimen for AL was developed in early trials showing that a six-dose regimen of AL taken twice per day, with the second dose taken after eight hours, resulted in higher cure rates than a four-dose regimen [34,37,38]. However, it is unclear how strictly dose intervals must be adhered to in order for treatment to be effective. For example, patients who obtain ACTs in the evening may be less likely to adhere to correct dose timing than patients who obtain ACTs in the morning, and it is unclear to what extent this matters. As adherence needs to be defined and measured depending on what is required for drug effectiveness, the importance of exact dose timing must be clarified.

Conclusion

Accurate measurements of patient adherence are important for developing strategies to assure the effectiveness of ACTs. While self-reported data along with examination of packaging might be sufficient to assess completion of treatment, patient reports of timely completion appear to be affected by both recall and/or social desirability bias. Smart blister packs provided slightly lower, and potentially more accurate, estimates of the number of pills taken for each dose and the time intervals between doses. In settings where data on dose timing are considered important for clinical outcomes, smart blister packs may be a useful tool, though innovations to make them more robust and discreet would be useful. Improved methods for collecting self-reported data are also likely to enhance the accuracy of measured patient adherence to treatment. Finally, a clearer rationale for what is considered adequate adherence is required.

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Table 1: Characteristics of patients with and without self-report and smart blister pack data available (percent (number))[1,2]

	Patients with smart blister pack data available (N=696)	Patients without smart blister pack data available (N=508)	p-value
Male	45.3 (315)	48.0 (244)	0.3
Age[3]			0.0249
Under 3 years	26.9 (187)	21.1 (107)	
3 years to under 8 years	23.8 (166)	21.3 (108)	
8 years to under 12 years	5.8 (40)	8.1 (41)	
12 years and above	43.5 (303)	49.6 (252)	
Patient (or caregiver if patient below age 12 years) completed primary school	70.9 (490)	71.0 (360)	0.9
Slept under net the night before the interview	72.2 (502)	76.7 (388)	0.1
Attended an outlet in an urban ward	47.6 (331)	50.8 (258)	0.4
Attended ADDO (vs. public health facility)	64.2 (447)	66.9 (340)	0.2
Distance of 2.5 km or less from home to outlet (by GPS coordinates)	73.9 (468)	75.2 (340)	0.6
Reported being tested for malaria at outlet	26.4 (183)	24.2 (122)	0.5
Reported taking first dose of AL at the outlet	22.8 (158)	17.4 (88)	0.0281
Reported receiving correct instructions on AL regimen[4]	59.6 (281)	57.3 (291)	0.4

[1] For patients with self-reported data and smart blister pack data available, data were missing for education for 5 patients, net use for 1 patient, GPS data for 63 patients, being tested for malaria for 2 patients, and taking the first dose of AL at the outlet for 4 patients.

[2] For patients without self-reported data and smart blister pack data available, data were missing for education for 3 patients, net use for 2 patients, GPS data for 73 patients, being tested for malaria for 5 patients, and taking the first dose of AL at the outlet for 2 patients.

[3] Age categories based on recommended age breakdown for AL blister packs in Tanzania.

[4] Reported the correct number of pills per dose, the correct number of doses per day, and the correct number of days per dispenser instructions.

Table 2: Completed treatment by self-report and smart blister packs

	Self-report	Smart blister packs
Number with self-reported data and electronic blister pack data available (N)	696	696
Percent completed treatment (numerator / denominator) (95% CI)		
Total[1]	**64.1 (446/696) (59.8, 68.1)**	**66.7 (464/696) (62.3, 70.7)**
1x6 (6 tablets)	65.1 (162/249) (58.2, 71.4)	65.5 (163/249) (58.8, 71.6)
2x6 (12 tablets)	64.5 (80/124) (55.9, 72.3)	66.9 (83/124) (58.2, 74.6)
3x6 (18 tablets)	53.7 (22/41) (39.8, 67.0)	61.0 (25/41) (46.0, 74.1)
4x6 (24 tablets)	64.5 (182/282) (58.6, 70.1)	68.4 (193/282) (62.2, 74.1)

[1]An odds ratio for the effect of measurement method on completed treatment could not be calculated because there were zero patients who reported completing treatment but did not complete treatment by smart blister pack data.

Table 3: Timely completion by self-report and smart blister packs[1] (percent (number))

	Self-report		**Smart blister packs**	
	Patients completing treatment	All patients	Patients completing treatment	All patients
Total	**418**	**641**	**436**	**641**
1x6 (6 tablets)	154	239	155	239
2x6 (12 tablets)	77	121	80	121
3x6 (18 tablets)	21	36	24	36
4x6 (24 tablets)	166	245	177	245
Percent taking the correct number of pills for each of six actual doses[2,3]				
Total	**96.9 (405)**	**63.5 (407)**	**67.2 (293)**	**45.7 (293)**
1x6 (6 tablets)	96.1 (148)	62.3 (149)	75.5 (117)	49.0 (117)
2x6 (12 tablets)	98.7 (76)	62.8 (76)	71.3 (57)	47.1 (57)
3x6 (18 tablets)	100 (21)	58.3 (21)	62.5 (15)	41.7 (15)
4x6 (24 tablets)	96.4 (160)	65.7 (161)	58.8 (104)	42.5 (104)
Percent taking six actual doses at the correct time intervals: [4,5]				
Total	**58.4 (244)**	**39.6 (254)**	**40.4 (176)**	**27.6 (177)**
1x6 (6 tablets)	57.8 (89)	38.1 (91)	32.9 (51)	21.3 (51)
2x6 (12 tablets)	58.4 (45)	38.0 (46)	36.3 (29)	24.8 (30)
3x6 (18 tablets)	71.4 (15)	44.4 (16)	54.2 (13)	36.1 (13)
4x6 (24 tablets)	57.2 (95)	41.2 (101)	46.9 (83)	33.9 (83)
Timely completion (Percent taking the correct number of pills at the correct time intervals for each of six actual doses):				
Total[6]	**57.4 (240)**	**37.4 (240)**	**35.6 (155)**	**24.2 (155)**
1x6 (6 tablets)	56.5 (87)	36.4 (87)	32.9 (51)	21.3 (51)
2x6 (12 tablets)	58.4 (45)	37.2 (45)	32.5 (26)	21.5 (26)
3x6 (18 tablets)	71.4 (15)	41.7 (15)	50.0 (12)	33.3 (12)
4x6 (24 tablets)	56.0 (93)	38.0 (93)	37.3 (66)	26.9 (66)

[1] 55 patients were excluded from this analysis because data on timing of each actual dose were not possible to assess for self-report for 18 patients and for smart blister pack data for 37 patients.

[2] "Actual doses" refers to pills actually taken together, including pills that were not grouped together, or a different number than specified for the intended dose. Pills administered at least 30 minutes apart from each other were considered different actual doses.

[3] By self-report, number of pills taken missing for one dose for 2 patients for the 1x6 pack, 1 patient for the 2x6 pack, and 8 patients for the 4x6 pack.

[4] By self-report, time of taking one or more doses missing for 24 patients for the 1x6 pack, 12 patients for the 2x6 pack, 2 patients for the 3x6 pack, and 20 patients for the 4x6 pack.

[5] By smart blister pack data, no patients who completed treatment and took more than six actual doses took the first six at the correct intervals.

[6] For all patients (total columns) the odds ratio for timely completion by smart blister pack vs. self-report was 0.36, 95% CI: 0.29, 0.42; $p<0.0001$.

Table 4: Median number of actual doses and pills taken by self-report and smart blister packs [1]

	Self-report			**Smart blister packs**		
	Patients completing treatment	Patients not completing treatment	All patients	Patients completing treatment	Patients not completing treatment	All patients
Total	**418**	**223**	**641**	**436**	**205**	**641**
1x6 (6 tablets)	154	85	239	155	84	239
2x6 (12 tablets)	77	44	121	80	41	121
3x6 (18 tablets)	21	15	36	24	12	36
4x6 (24 tablets)	166	79	245	177	68	245
Median (range) number of actual doses taken[2]						
Total	**6 (6-6)**	**5 (0-6)**	**6 (0-6)**	**6 (1-8)**	**4 (0-7)**	**6 (0-8)**
1x6 (6 tablets)	6 (6-6)	4 (1-5)	6 (1-6)	6 (1-6)	4 (1-5)	5 (1-6)
2x6 (12 tablets)	6 (6-6)	4 (0-5)	6 (0-6)	6 (1-7)	4 (1-7)	6 (1-7)
3x6 (18 tablets)	6 (6-6)	5 (2-6)	6 (2-6)	6 (1-8)	5 (2-6)	6 (1-8)
4x6 (24 tablets)	6 (6-6)	5 (0-6)	6 (0-6)	6 (1-8)	5 (0-7)	6 (0-8)
Median (range) number of pills taken[3,4]						
1x6 (6 tablets)	6 (6-7)	4 (1-6)	6 (1-7)	6 (6-6)	4.5 (1-5)	6 (1-6)
2x6 (12 tablets)	12 (12-13)	8 (0-12)	12 (0-13)	12 (12-12)	8 (1-11)	12 (1-12)
3x6 (18 tablets)	18 (18-18)	15 (6-15)	18 (6-18)	18 (18-18)	13.5 (6-15)	18 (6-18)
4x6 (24 tablets)	24 (24-24)	20 (0-24)	24 (0-24)	24 (24-24)	20 (0-22)	24 (0-24)

[1] 55 patients were excluded from this analysis because data on timing of each actual dose were not possible to assess for self-report for 18 patients and for smart blister pack data for 37 patients.

[2] "Actual doses" refers to pills actually taken together, including pills that were not grouped together, or a different number than specified for the intended dose. Pills administered at least 30 minutes apart from each other were considered different actual doses.

[3] By self-report, number of pills taken was missing for one dose for 2 patients for the 1x6 blister pack, 1 patient for the 2x6 blister pack, and 8 patients for the 4x6 blister pack.

[4] 6 patients reported taking all pills, but since pills remained in the blister pack, they were not considered to have completed treatment (4 patients taking the 1x6 pack, 1 patient for the 2x6 pack, and 1 patient for the 4x6 pack). 1 patient for the 2x6 pack and 2 patients for the 4x6 blister reported taking no actual doses.

Figure 1: Picture of a smart blister pack showing resemblance to regular blister packs

Figure 2: Flow chart of patients included in analysis

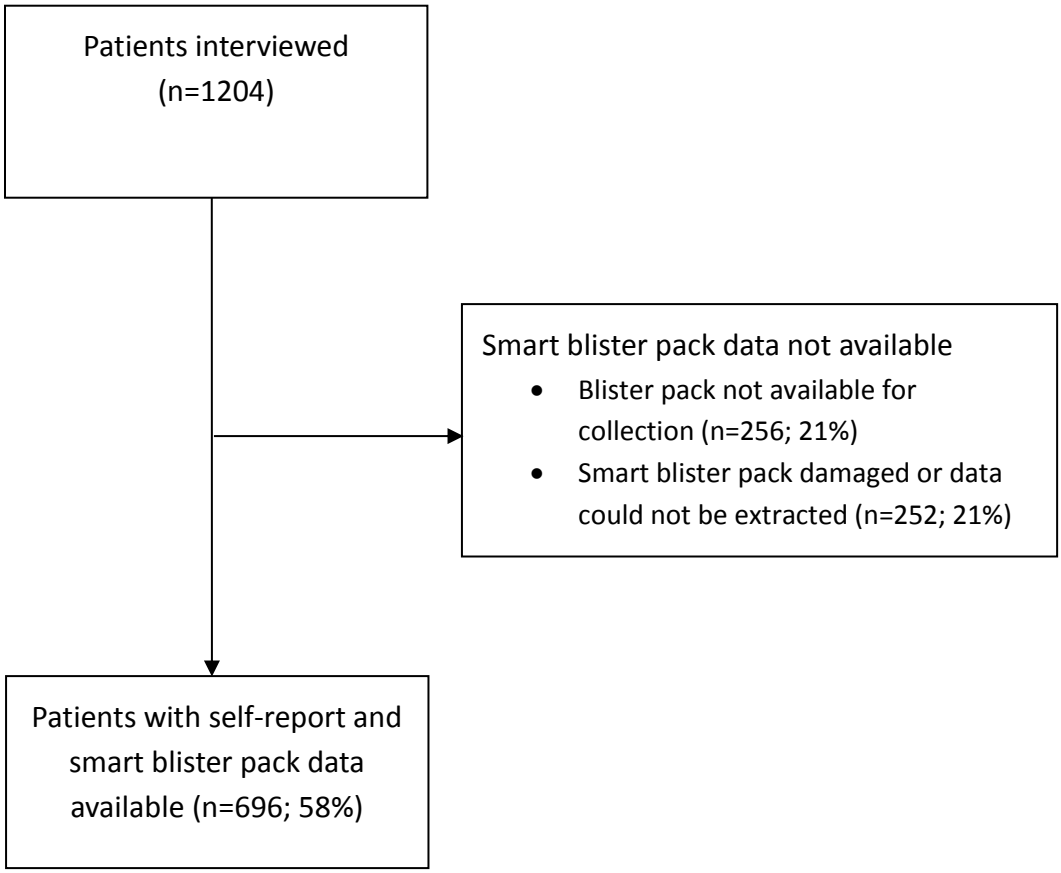
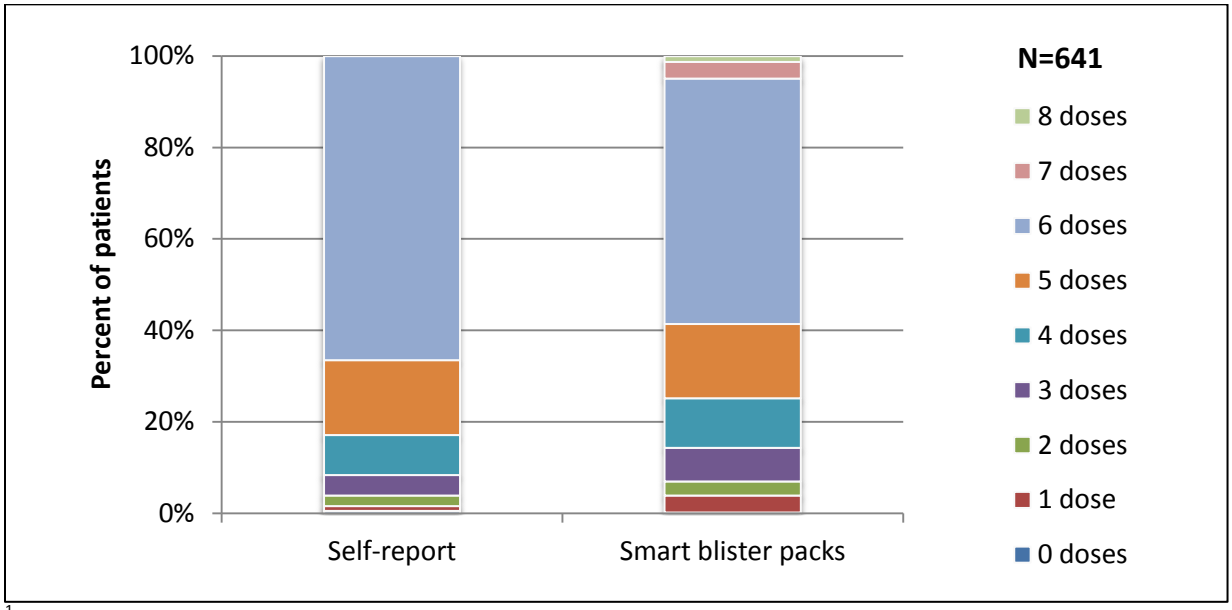


Figure 3: Number of actual doses taken by self-report and smart blister packs[1-3]

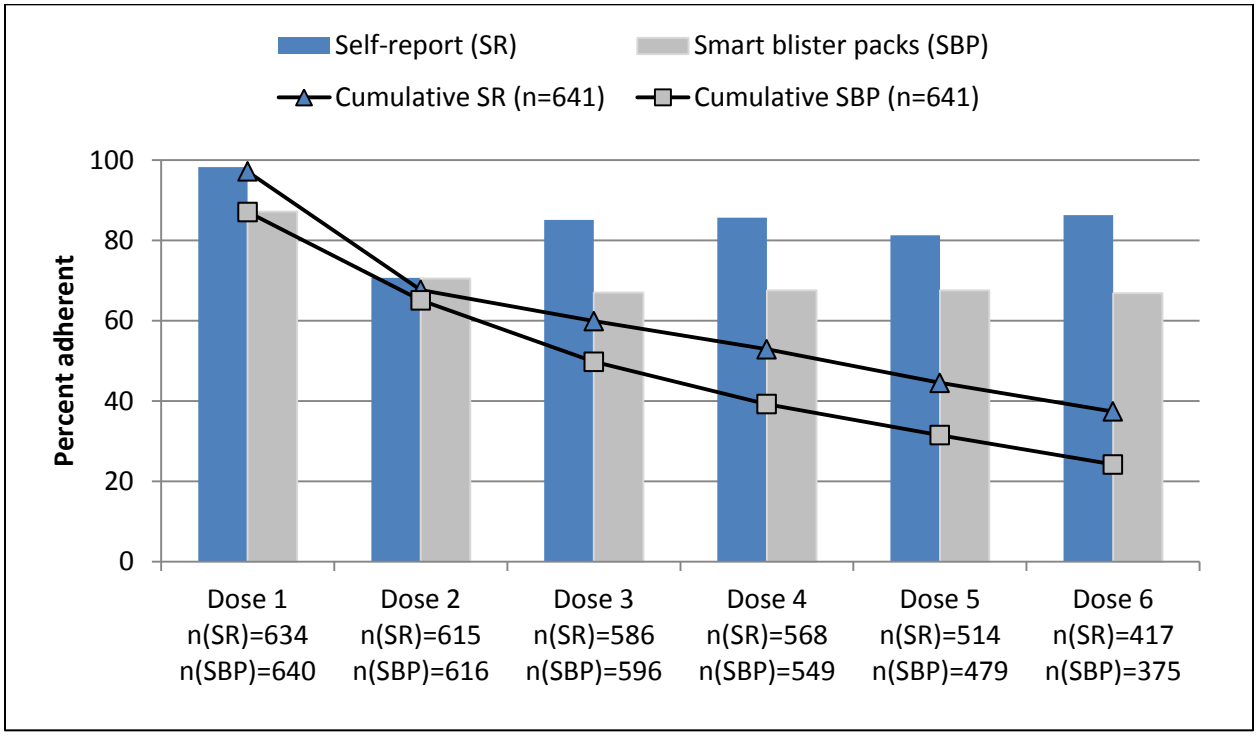


[1]55 patients were excluded from this analysis because data on timing of each actual dose were not possible to assess for self-report for 18 patients and for smart blister pack data for 37 patients.

[2]"Actual doses" refers to pills actually taken together, including pills that were not grouped together, or a different number than specified for the intended dose. Pills administered at least 30 minutes apart from each other were considered different actual doses.

[3]By self-report, patients were asked only about each of the six intended doses.

Figure 4: Timely completion for each actual dose and cumulatively[1]



[1]55 patients were excluded from this analysis because data on timing of each actual dose were not possible to assess for self-report for 18 patients and for smart blister pack data for 37 patients.

Supporting Information Table 1: Matrix of completing treatment showing sensitivity and specificity of self-report compared to smart blister pack data

Percent (number)
(95% CI)

		Smart blister packs		
		Completed treatment	Did not complete treatment	Total
Self-report	Completed treatment	96.1 (446) (93.6, 97.7)	0	64.1 (446) (59.8, 68.1)
	Did not complete treatment	3.9 (18) (2.32, 6.42)	100 (232)	35.9 (250) (31.9, 40.2)
	Total	100 (464)	100 (232)	100 (696)

Supporting Information Table 2: Matrix of timely completion showing sensitivity and specificity of self-report and smart blister pack data

Percent (number)
(95% CI)

		Smart blister packs		
		Timely completion	No timely completion	Total
Self-report	Timely completion	73.5 (114) (66.1, 79.8)	25.9 (126) (21.7, 30.6)	37.4 (240) (32.8, 42.3)
	No timely completion	36.5 (41) (20.2, 33.9)	74.1 (360) (69.4, 78.3)	72.6 (401)
	Total	100 (155)	100 (486)	100 (641)

8 Discussion

The final chapter of this thesis summarises the main findings of the research, discusses strengths and limitations, and considers the implications of this work for policy and future studies.

Table 1 Synthesis of key thesis results

Key results	Interpretation & implications
Adherence in public health facilities and ADDOs **Levels of adherence[1] in public health facilities and ADDOs, respectively:** Completed treatment: 75% & 70% (p=0.2) Timely completion: 46% & 35% (p=0.003) **Adjusted odds ratios[2] for ADDO patients vs. public health facility patients:** Completed treatment: 0.65 (95% CI: 0.43, 1.00) Timely completion: 0.69 (95% CI: 0.47, 1.01)	There was limited evidence of lower adherence among patients attending ADDOs vs. public health facilities, although the reasons for this were not clear. Interventions to improve care for malaria patients are needed in both sectors.
Text message intervention targeted at ADDO dispensers to improve patient adherence to AL **Levels of adherence[1] in intervention and control arms, respectively:** Completed treatment: 68.3% & 69.8%, (p[adjusted]=0.6) Timely completion: 33.1% & 32.6% (p[adjusted]=0.9)	A text message intervention targeted at ADDO dispensers was not successful in improving patient adherence. The potential of other interventions depends on the true reasons for non-adherence, which are still poorly understood.
Comparison of patient adherence measured by self-report and smart blister packs **Levels of adherence[1] by self-report and smart blister pack data, respectively:** Completed treatment: 64% & 67%[3] Timely completion: 37% & 24% (p<0.0001)	Self-reported data may overestimate verified timely adherence compared to smart blister pack data. Improved smart blister pack designs may be useful for future studies where precise data on dose timing are needed.
Existing concepts of adherence	Caution should be used when comparing adherence levels across studies, as differences in study design and approach to assessing adherence can influence results. Better understanding is needed of how adherent patients must be for treatment to be effective, particularly in terms of dosing schedule and fatty food intake. Guidance on dosing schedules for patients who obtain AL in late afternoon or evening needs to be determined and should be clearly communicated to providers and patients.

[1]Verified by pill count when available
[2]Adjusted for patient characteristics
[3]A p-value for the effect of measurement method on completed treatment could not be calculated because there were zero patients who reported completing treatment but did not complete treatment by smart blister pack data.

8.1 Summary of findings

In addition to undertaking an updated systematic review on adherence to antimalarial drugs, the objectives of this thesis were to (1) determine differences in patient characteristics and levels of adherence between patients obtaining AL in public health facilities and ADDOs, and to examine factors associated with adherence in both of these settings; (2) evaluate the effect on dispenser knowledge and patient adherence of text message reminders targeted at ADDO dispensers concerning advice to provide when dispensing AL; and (3) compare the validity of assessing patient adherence with self-reported data compared to smart blister packs. A summary of key results and their interpretation and implications is shown in Table 1 and referred to throughout this chapter.

In Chapter 2, a published literature review and addendum in Chapter 2.3 described all studies of adherence to antimalarial drugs through September 2014. Extensive variation was observed in levels of adherence, with some studies reporting high adherence above 90%, and others reporting extremely suboptimal adherence of less than 50%. Among studies of adherence to ACTs, results ranged from 7%-100%.

Because results may vary depending on the relative lenience of the definition of adherence, five approaches for assessing adherence were identified: Completed treatment, verified completed treatment, timely completion, verified timely completion, and biological assays. All but 6 of the 67 studies (including those added in Chapter 2.3) used one or more of these approaches, with the remaining six using only unique approaches. While the diversity of study drugs, settings, and factors related to study design made it difficult to identify systematic differences in adherence between approaches, among studies of AL there was a weak indication that studies using pill counts had lower adherence.

The review also demonstrated that patient interaction with research staff may increase social desirability bias. Studies where patients had given informed consent prior to taking treatment and those

where consultations had been observed by research staff tended to report higher adherence. In addition, studies where there was a larger research presence (e.g. effectiveness trials with multiple follow-up visits) often reported higher adherence. Studies where patients had been tested for malaria prior to obtaining AL and those where the first dose was taken under observation also reported higher adherence. However, these practices were often part of the research protocol, so it is unclear if the same effects would be seen under routine conditions.

As the majority of studies reporting adherence to ACTs were conducted in the public sector, even though ACTs are now also available in the private for-profit sector, we conducted two parallel and contemporaneous studies in public health facilities and ADDOs to compare adherence to AL between these outlet types (the first research objective, reported in Chapter 6). As summarised in Table 1, adherence in both sectors was suboptimal, with verified completed treatment of 75% among health facility patients and 70% among ADDO patients (p=0.2) and verified timely completion of 46% among health facility patients and 35% among ADDO patients (p=0.003). In comparison to other studies of AL in public health facilities in Tanzania, verified completed treatment in our study was similar to two other studies (with and without pill counts) (77%-80%) [1, 2], but verified timely completion was lower than in three other studies (75%-90%) [3-5] and higher than in another study (7%) [2]. Adherence has not been previously assessed from drug stores in Tanzania, though verified completed treatment in our study was similar to levels of completed treatment (without pill count) in a household survey in Tanzania (69%) and a study from drug stores in Uganda (66%) [6].

Characteristics of patients varied substantially between sectors, with those attending ADDOs wealthier, more educated, older, visiting the outlet later in the day, and less likely to have malaria than health facility patients. When controlling for patient characteristics, there was some evidence that adherence by both measures was lower among ADDO patients than health facility patients. In both sectors, recalling correct advice on how to take AL was associated with both verified completed

treatment and verified timely completion. In health facilities, taking the first dose of AL at the outlet was associated with verified timely completion (but not verified completed treatment).

In order to address concerns about lower adherence to ACTs obtained in the private retail sector, we conducted a cluster-randomised trial of a text message intervention to improve dispenser knowledge and patient adherence (second research objective, Chapter 5). While the intervention was delivered effectively, the text messages only had some effect on dispenser knowledge (e.g. taking with fatty food and continuing treatment if minor side-effects occurred) and had no effect on advice patients reported receiving or on patient adherence. Verified completed treatment was 68.3% and 69.8% in the intervention and control arms, respectively (p [adjusted] = 0.6), and verified timely completion was 33.1% and 32.6%, respectively (p [adjusted] = 0.9) (Table 1).

One possible reason for the lack of observed effect could be the recent training on treatment of malaria with ACTs in the study site, and therefore relatively high knowledge among dispensers in both arms. It is also possible that gaps in dispenser knowledge were not addressed by the content of the messages, and that dispensers did not increase the advice they provided to patients, as they were deliberately not told that the reason for the messages was to increase adherence. Alternatively, patients may have had poor recall of the advice or were otherwise unreceptive to extra advice received. Patients in both arms did report receiving some advice, but the relative roles and impact of advice and other determinants of adherence remain unclear.

In Chapter 7, the third research objective of comparing methods to assess adherence, was examined. There was no difference between self-reported adherence and smart blister pack data for verified completed treatment, but verified timely completion was lower by smart blister pack data (Table 1). While self-reported data are cheaper and easier to collect, their results for timely completion were prone to patient confusion, poor recall, and social desirability bias. Smart blister packs provided more accurate information on how each actual dose was taken, though a large number of smart blister

packs were damaged and did not allow for extraction of data. Because of these missing data, self-report was used to report adherence for the CRT and observational study in public health facilities. The results of the smart blister pack data in Chapter 7 suggest that the estimates of self-reported completed treatment presented in these research papers (Chapters 5 and 6) were likely accurate, but that timely completion may have been over-estimated. A third method of assessing adherence, quantification of lumefantrine concentrations from filter paper dried blood spots, was not successful, most likely due to the lengthy time of storage prior to analysis.

8.2 Thesis strengths and limitations

This section reviews key strengths and limitations of the research papers in Chapters 2, 5, 6, & 7 and focuses on strengths and limitations of the thesis as a whole. The first part of the section (8.2.1) highlights the work on definitions of adherence and methods of data collection, while the second part (8.2.2) addresses the private for-profit sector, and the third section (8.2.3) draws these together to consider the evaluation of the text message intervention in ADDOs.

8.2.1 Adherence definitions and methods

Throughout the thesis a key theme has been the methodological challenges of assessing adherence. These relate to both defining adherence itself and to the techniques for recording it. Challenges of comparability of definitions with other studies and limiting sources of bias are also important considerations.

Definitions of adherence. The literature review in Chapter 2 identified five approaches to assessing adherence to antimalarials that encompassed the approaches used in 61/67 of studies (see Table 4 in Chapter 2.2). This categorization scheme is useful for identifying patterns in results and facilitating further discussions on comparing adherence across settings. However, within these general

approaches, there is variation in how completion and timeliness are defined, and how pill counts are incorporated. For example, for AL, completion could mean completing the course of treatment obtained or completing the correct course of treatment based on patient weight, or completing all doses within 4 days, or completing all doses by the time of the follow-up visit. Similarly, timeliness could include, for example, taking two doses per day morning and evening for three days or taking the correct number of pills at the correct times for each of six doses. Furthermore, timeliness could involve taking the second dose after 8 hours (as opposed to 12 hours), allowing several hours more or less for each correct interval. As noted in Table 1, these variations affect comparability between studies, as within a single study, each variation could yield a different result.

In the studies presented in the research papers in Chapters 5 and 6, we opted to evaluate adherence to the AL pack obtained, rather than to the pack that corresponded to the patient's age, which would have combined both dispenser and patient behaviour and been more difficult to interpret. However, some patients did obtain incorrect doses; 15% of the 249 patients with self-report and smart blister pack data that obtained a 1x6 pack were older than three years, although some of these may have been small for their age. Patients were followed up on day 4, as this is most consistent with treatment recommendations and with follow up periods used in other studies. A further strength is the use of Swahili times of day to assess timeliness, which were thought to be more accurate than asking for exact times, as patients are unlikely to recall exact times and do not typically use clocks or watches. The validity of this approach was confirmed by matching reported times of day with exact times from smart blister pack data for patients with verified timely completion by both self-report and smart blister pack data. However, it is unclear if and how this approach could be applied to other countries.

Limiting sources of bias. An important emphasis in this thesis was the careful use of strategies in study design and data collection to limit sources of bias. For example, in selecting ADDOs for the CRT, a buffer zone was required between control and intervention outlets, although the limited number of

shops restricted this distance to only 400 meters (Appendix 3a). A large number of outlets (77 ADDOs and 40 public health facilities) were enrolled so that a small number of patients from each shop could be registered over a short period of time (1-3 weeks); this was done to lessen community awareness of the study that might have impacted behaviour. Since the literature review indicated that requesting informed consent at the outlet and observation of the dispenser-interaction could result in increased Hawthorne bias, study staff had no interaction with patients and limited their presence at the outlet to a short visit once per day to collect forms. Similarly, dispensers were not told that the purpose of the messages or the intent of the evaluation was to assess adherence. They were asked to register all patients obtaining a drug for fever or malaria, not just ACTs, and to provide minimum details about the possibility of a home visit from study staff (Appendix 1a-b). Informed consent was not requested of patients until they were visited on day 4.

We attempted to limit recall bias by visiting patients as soon as possible three days after treatment should have been completed (day 4). We estimated the time of the visit to be 68-72 hours after the drug was obtained, but there was a large degree of uncertainty due to challenges with dispensers recording the time the drug was obtained and field logistics. In order to improve our chances of blister pack recovery, we erred on visiting earlier rather than later on day 4, but this meant more patients obtaining AL at ADDOs compared to health facilities were visited between 60-67 hours (this was controlled for in the analyses in Chapter 6). The data collection tool was designed to talk patients through each dose, and Swahili times rather than exact hours likely improved recall, but accounts of some patients were still inconsistent. An alternative strategy would be to visit patients daily, but this would result in a much greater Hawthorne effect. Other studies have randomised patients to different follow up times during the course of the treatment [3, 5]. While this approach might provide more accurate information about early doses, results become difficult to compare with studies that visit patients after treatment is expected to be complete.

Patients may have responded to questions about adherence dishonestly in order to appear less negligent, or may have answered other questions according to their perception of the "expected" or "correct" response (e.g. results of an RDT conducted at the outlet). To limit this social desirability bias, patients were told when explaining the consent form prior to interview that the purpose of the visit was to understand how people in the region prefer to take medicines in order to improve malaria services. Patients were also asked for blister packs at the end of the interview so that they would not attempt to make their accounts match with the blister packs (however, pills could still have been removed prior to presenting the packs).

Use of smart blister packs. This thesis reports the first time that smart blister pack technology has been applied to antimalarials. It is also the first time that smart blister packs have been designed and used with the intent of patients being unaware of adherence monitoring until the follow up interview, which was important for avoiding a Hawthorne effect and assessing the validity of self-report. The smart blister packs enabled collection of accurate and specific data on when each pill was removed from the blister pack. These data are useful in understanding patterns of non-adherence, including errors in the number of pills taken for each dose, the number of actual doses taken, and the number of hours between each dose. The research paper in Chapter 7 constitutes the most detailed report in the literature to date of how ACTs are taken.

Despite the novel advantages of the smart blister packs, there were several notable issues. First, while the packs were easy to assemble and graphically looked identical to the Coartem® available in Tanzania, the slight bulge of the data chip was more prominent than in the samples provided by the company as examples. Due to the expense of the smart blister packs and time constraints, we were not able to pilot the final smart blister pack product prior to the study. The majority of dispensers and patients did not notice or were not concerned with the slight bulge in the packaging. However, some patients did become suspicious and open the packs to investigate. In several villages in one district

(Tandahimba), the positive sign on the small battery component of the chip was interpreted to be a symbol of the highly distrusted free masons group, angering some community members and causing suspicion of the research teams. However, village leaders, dispensers, and affected community members were receptive to meetings held with study leaders explaining the design of the blister packs and research objectives as a whole, and the study was able to continue.

Although approximately 20% of patients had damaged blister packs, this appeared to have only a minimal impact on results. Self-reported completed treatment was actually slightly higher for patients with damaged packs compared to those with smart blister pack data available, and was not different from self-reported completed treatment among a similar number of patients that had obtained regular packs (dispensed from outlets' own stock or provided by the study team when supplies of smart blister packs ran low). One of the main reasons given for damaged packs was that children had been allowed to play with them following treatment. The majority of patients with intact smart blister packs had not noticed the special nature of the pack, and very few patients (less than five) gave concern over the pack as a reason for not completing treatment.

Following completion of our research, meetings were held with leaders in each administrative division of Tandahimba district by IHI to discuss community concerns and perceptions about research conducted by IHI projects. A newsletter about IHI and details of our studies was distributed, including information on the smart blister packs. The majority of concerns raised at the meetings were about clashes with the government regarding cashew crop payments and various general questions about malaria, maternal health, and HIV. The association of IHI with free masons was mentioned only briefly in one division and appeared to have not caused widespread concern.

A second challenge with the smart blister packs was realised during the analysis phase, when data were laborious to work with. According to our design, a separate timestamp was recorded for each tablet. However, these timestamps had to be grouped manually into doses, which may have

inadvertently introduced error. Had we been able to pilot the smart blister packs, it is possible that we could have worked with the company to design a relatively simple programming solution that would have made the data easier and quicker to work with. This should be considered by any future projects that use smart blister packs for ACTs.

Measuring blood levels of lumefantrine. In addition to the use of smart blister packs, we also collected dried blood spot filter papers for analysis of lumefantrine concentrations. These data could have been a great asset to the research paper comparing methods of assessing adherence (Chapter 7). Following data collection, filter papers were stored for 19-24 months, mostly in Switzerland, while waiting for equipment and funding for the analysis to become available. When finally analysed, most filter papers had lumefantrine concentrations below the lower limit of quantification. As the methods used in the lab had been previously validated, either the storage conditions or the lengthy period prior to analysis are the most likely reasons for the poor lumefantrine recovery [7].

8.2.2 Studying the private for-profit sector

The research paper in Chapter 6 represents one of the first studies to report adherence to antimalarial drugs obtained in the private for-profit sector and to follow-up and compare patients attending outlets in both public and private sectors, which is important given the role of the private for-profit sector in provision of antimalarials [8]. This was also the first study to examine adherence to antimalarial drugs in ADDOs. In Tanzania, ADDOs are a major source of antimalarial drugs [9], and the ADDO model has been cited as an example for regulation of drug stores in other countries [10]. In addition, this was one of the first studies to assess adherence to AMFm co-paid ACTs, helping to address a gap in evidence that was not considered in the AMFm Independent Evaluation [11]. Another recent study including both public and private for-profit outlets was conducted in Ghana, where AMFm-

subsidised drugs were also available [12][1]. This study reported a slightly lower percentage of patients completing treatment compared to our study (62%, compared to 70% in ADDOs).

One limitation of our study comparing adherence to AL obtained in public health facilities and ADDOs is that dispenser interviews were not conducted at health facilities. A frequently raised concern regarding treatment of malaria in the private retail sector is that dispensers may be less qualified than health facility dispensers and have less training and lower knowledge on treatment of malaria with ACTs [13]. In the analysis examining the effect of sector on patient adherence, we controlled for patient characteristics. It would have been interesting to also examine the effect of outlet-level and dispenser characteristics in sector-specific models, as done for patient report of factors related to care and advice received. In addition, this thesis did not address adherence to ACTs obtained at other less common sources of antimalarials, such as mission facilities, pharmacies, general shops, and community health workers.

8.2.3 Evaluation of the text message intervention in ADDOs

Chapter 5 reports one of the first intervention studies to improve patient adherence to ACTs obtained in the private for-profit sector. (Two other similar randomised controlled trials have recently been conducted and will be discussed in Section 8.3 below.)

Text message intervention. The strengths and limitations of the text message intervention are considered in detail in the research paper in Chapter 5. As discussed in Section 8.1, one important finding was that dispenser knowledge in the control arm was higher than expected, which might have been partly due to the recent refresher training in Mtwara that had covered ACTs. While knowledge of the message content was evaluated at the dispenser level, several of the messages (e.g. taking the first dose under observation at the outlet, taking with fatty food, and obtaining a replacement dose in case

[1] This study was not included in the literature review in Chapter 2, including the update in Chapter 2.3, as it was not published by the end of September 2014.

of vomiting) were not part of the verified completed treatment and verified timely completion outcome measures (although these characteristics are described for both ADDO and public health facility patients in Chapter 6).

Strengths and limitations of study and evaluation design. The study was designed as a CRT, with the text message intervention randomly allocated at the cluster level (ADDOs). The advantages of this study design include reducing selection bias and confounding through the random allocation of the intervention and minimizing contamination between control and intervention arms. However, this design and additional efforts to limit potential Hawthorne effects and recall bias likely caused the evaluation setting to be different than if the intervention was applied in a programmatic setting, as the latter might involve being more explicit about raising awareness about adherence in both the shops and the community.

Secondly, the intervention was evaluated by patient interviews, followed by dispenser interviews. These methods were chosen to assess the effect of the intervention on both dispensers and patients, while limiting potential sources of bias. However, the evaluation might have been strengthened by the inclusion of additional types of data collection. For example, exit interviews might have provided insight into where the intervention broke down- either at the point of dispenser communication with patients, or with patients' subsequent recall and behaviour. Mystery clients might have allowed us to more accurately assess dispenser communication. Qualitative data collection could also have been useful for understanding perceptions of dispensers and patients, why some advice was not communicated, and why some patients were non-adherent.

8.3 Thesis implications

This section begins by examining the importance of adherence for treatment effectiveness. Implications related to comparing adherence studies and measuring adherence are then discussed,

followed by possible reasons for differences in adherence between sectors and generalizability of these results. Finally, potential interventions to improve adherence are considered.

Does adherence matter? "Drugs don't work in patients who don't take them." This quote from C. Everett Koop, cited in a review of adherence to medication across diseases [14], reflects a concept mentioned ubiquitously in studies on adherence to antimalarials. This thesis also states that patient adherence to ACTs is important in order to avoid treatment failure and limit resistance to ACTs. However, as mentioned in Chapter 1, there is very little data on how adherent patients must be in order to avoid treatment failure.

Early trials indicated that a four-dose regimen of AL was less effective than a six-dose regimen [15, 16]. One trial compared the four-dose regimen to a 3 day six-dose regimen and a 5 day six-dose regimen and found day 28 cure rates of 83.3%, 96.9%, and 99.1% [17]. While there was a significant difference between the four-dose regimen and the six-dose regimens, there was no difference between the two six-dose regimens, as also reported by a second study comparing these three regimens, over a 42-day follow-up period [18]. Interestingly, most studies of adherence to AL, including those reported in this thesis, interview patients on day 4 (Chapter 2), categorising patients that would have finished AL within 5 days as non-adherent. Although patients taking the six-dose regimens were shown to have higher day 7 lumefantrine levels than those taking the four-day regimen [18], sufficient therapeutic levels of drug can still be achieved in many patients in less than six doses.

Studies examining differences in treatment effectiveness between adherent and non-adherent patients have not reported significant differences [19-21]. While one study reported slightly higher treatment failure rates to artesunate-mefloquine in an unsupervised group compared to a supervised group (3.9% vs. 0.0%, p=0.015) [22], studies of AL have not [21, 23, 24]. This may be due to very high adherence (>90%) and / or very high cure rates (>95%) in both supervised and non-supervised groups. Additional studies are required in which adherence and effectiveness are assessed but with minimal or

no interaction with study staff prior to taking the treatment course. This is challenging, as malaria must be confirmed in these patients at the time of obtaining treatment, and consent must be requested from patients prior to collecting blood samples. Patients must also be monitored for treatment failure for 42 days. As demonstrated in Chapter 2, greater interaction with study staff and awareness of the research are likely to inflate adherence.

This study did not assess the effectiveness of treatment obtained. The study aimed to assess adherence to AL obtained routinely from ADDOs and health facilities, and thus two-thirds of the patients who obtained AL tested negative by RDT performed by the study team on day 4 and probably did not have malaria at the time of seeking care. Of 1,422 patients from both sectors combined, 35.5% were RDT positive and 2% were positive by reference blood smear collected on day 4. There was no difference between adherent and non-adherent patients in the percentage of patients testing positive by RDT that had a positive blood smear (Chapter 6.3). While this indicates good parasite clearance for both adherent and non-adherent patients, a much longer follow-up period (e.g. to 42 days) would have been required formally to assess treatment failure.

While completing six doses may not be essential for all patients, it is likely necessary on a population level, as the recrudescence rates in the four-dose regimen were unacceptably high in some settings [18, 25]. It is also important to limit the proportion of patients that are exposed to sub-therapeutic levels of treatment, which can select for resistant parasites [26, 27]. However, the rationale behind exact timing of doses is less clear. The recommended schedule for each dose is 0, 8, 24, 36, 48, and 60 hours, also described as “at the time of diagnosis, 8 hours later, and then twice daily (morning and evening) on each of the following two days” [28]. The schedule is presumably derived from the concentration profiles of the partner drugs, although likely selected to a degree to conveniently fit six doses within three days. In this thesis, verified timely completion was much lower than completed treatment. Depending on the importance of timely completion for effectiveness, this may or may not be

of major concern. As national guidelines and interventions are implemented to improve timely completion, the basis behind the recommended regimen must be clarified (Table 1).

Similarly, intake of a small amount of fat with AL has been shown to affect lumefantrine absorption. According to the WHO Guidelines for the Treatment of Malaria, it is essential for patients and caretakers to be informed that they should take AL immediately after a meal or drink containing at least 1.2 g of fat [29]. However, in Tanzania the national guidelines specify taking AL with food and are ambiguous as to whether or not the food must contain fat [30, 31]. In the studies reported in this thesis, dispenser knowledge of the need to take AL with fatty food was significantly lower in the control arm (20%) than in the intervention arm (60%), and less than 10% of both public health facility and ADDO patients took all six doses with fatty food or milk. If taking each dose with fat is essential to effectiveness, as stressed by the WHO guidelines, then this message must be communicated more clearly across health sectors. The relative importance for effectiveness of AL should also determine if fat intake should be incorporated into adherence definitions, similar to the inclusion of dose timing discussed above. On the other hand, there could be potential confusion with instructions for DHA-piperaquine, the second-line treatment in Tanzania, which according to national guidelines should be taken with water only and no food to minimise the risk of adverse cardiac events [31, 32].

Comparing adherence studies. The literature review in Chapter 2 showed wide variation in adherence studies and makes clear that adherence studies are not all equal. Studies conducted under routine conditions cannot be compared to clinical trials or other studies where patients are subject to more interaction with study staff, testing, and careful monitoring. Comparing studies using different definitions or approaches to assessing adherence is also problematic. Even among similar studies, for example those assessing completed treatment or timely completion, the number of days of follow up allowed or the stringency of time intervals considered correct can alter adherence levels, which must be taken into account when interpreting results. Future studies reporting adherence need to be very

specific about the objectives, methods, and generalizability of results, and caution should be used when comparing results across studies (Table 1).

How to measure adherence. Self-reported data on adherence is the most feasible and least-expensive method of data collection. Compared to smart blister packs, we found good sensitivity and specificity of self-reported completed treatment. However, both sensitivity and specificity of self-reported timely completion were suboptimal (both 74%). Smart blister pack data provided more accurate data on when each pill was taken, which would be useful for studies where this type of data is needed. It also showed that both taking an incorrect number of pills and taking them at incorrect times contributed to non-adherence. However, the expense and some of the challenges encountered in the field may not make smart blister packs ideal for routine measurement of adherence.

Collection of self-reported adherence data needs to be improved in order to yield less biased and more accurate results. Limiting interaction with study staff and requesting informed consent at the time of the follow up interview when possible may reduce patient awareness of their adherence being monitored. Shorter time periods for running the study at each outlet might limit awareness in the community of study objectives and thus also help avoid a Hawthorne effect. Pill counts conducted at the time of interview are probably beneficial to avoid over-report of adherence, though evidence of this is limited (Chapter 2.3). Finally, further work is needed to assess the most appropriate way of asking dose-specific questions so as to avoid leading questions and patient confusion. Standard adherence definitions and approaches that minimise potential Hawthorne effects should also be agreed upon. This could possibly involve the development of a standardised questionnaire, although cultural factors such as different concepts of time could make this challenging.

Adherence in the public and private for-profit sectors. As mentioned above, this was one of the first studies to assess adherence to ACTs from the private for-profit sector. Although adherence was low in both sectors, our study found some evidence that adherence was lower in ADDOs (Table 1). There are

several possible explanations for this. First, dispenser characteristics, such as training on ACTs, might have been lower among ADDO dispensers, resulting in provision of less or poorer quality advice to patients. However, both public health facility and ADDO patients reported receiving similar levels and types of advice on how to take AL. Lower training or other factors could have affected the dispenser rapport with patients, and advice might not have been expected or followed [33].

Secondly, public health facility patients were more likely to actually have malaria and may have been more ill and therefore more likely to take treatment. However, it is difficult to discern which patients were most ill from patients' report of symptoms, none of which were associated with adherence. More than 90% of patients reported having had fever, while more public health facility patients reported respiratory symptoms (14% vs. 7.5%, p=0.007), and more ADDO patients reported body pain (30% vs. 15%, p<0.0001) and fatigue (18% vs. 10%, p=0.003). Very few patients reported convulsions, though this was significantly higher in public health facility patients (2.5% vs. 0.4%, p=0.007). At interview on day 4, more than 90% in both sectors reported they could work or play. As an alternative to asking about the presence or absence of specific symptoms, a recent study of adherence to AL from drug shops in Uganda used ladder scales from 1-10 to help patients gauge symptom severity (Cohen *et al.*, in draft)[2]. The study found that patients reporting having had more severe symptoms halfway through the treatment course were more likely to complete treatment.

A third potential reason for the difference in adherence between sectors is that more patients took the first dose of AL at health facilities compared to ADDOs (41% vs. 10%, p<0.0001), which might have started patients out on the right track. Although more patients were tested at health facilities (54% vs. 11%, p<0.0001), there was no clear association of the effect of testing on adherence in either sector. Further attention should be given to understanding these dynamics and differences between sectors in order to best target interventions to optimise care.

[2] This study was not included in the literature review in Chapter 2, including the update in Chapter 2.3, as it has not yet been published (December 2014).

One could argue that lower adherence in ADDO patients could be a reason not to continue a subsidy of ACTs in these outlets. However, the differences in adherence levels were not so large and, as noted above, the reasons for the differences remain unclear. Moreover, even if subsidised ACTs were not available in ADDOs (as was previously the case) patients would likely continue to seek care at these outlets, but obtain less effective antimalarials.

The findings described are likely generalizable to much of rural and peri-urban Tanzania, although generalizability to ADDOs in urban areas, which were not evaluated in our studies, is less clear. Although ADDOs have been scaled up nationwide, ADDOs in some areas received less training on ACTs, which could negatively impact advice dispensed and patient adherence in the absence of an intervention. ACTs might also not be as available or as affordable now compared to 2012, and the effects of training and community sensitization conducted around AMFm could be weakened. It is also unclear how generalizable these results are to other countries with similar drug stores, as other contextual factors could affect adherence. However, the two other studies of adherence to ACTs in drug stores mentioned above have reported only slightly lower completed treatment (66% in Uganda and 62% in Ghana, compared to 70% in our study) [6, 12].

Interventions to improve adherence. The private retail sector is a major source of treatment for malaria in Tanzania and in many malaria-endemic countries [34-38], and this is likely to continue. In both sectors, but particularly the private retail sector, interventions are needed to improve patient adherence to ACTs (Table 1). Although the text message intervention evaluated in this thesis did not have an impact on adherence, a similar intervention may still have potential for improving dispenser knowledge and encouraging provision of information to patients. Text messages to dispensers might be more effective with additional piloting, and in a setting where dispensers have not received recent training. The potential of utilising text messages should continue to be explored, given the low cost and relative ease of implementing this type of intervention, and the positive effects observed with health workers in

Kenya [39]. In this study by Zurovac *et al.* (discussed in Chapter 5.2), estimated costs under trial conditions were $0.50 per additional child correctly managed, with $98,000 needed for national scale up (only 1% of Kenya's Global Fund award to strengthen malaria case-management) [40].

Other studies are examining the effect of text messages targeted directly at patients. The study by Raifman (Goldberg) *et al.* in Ghana in public and private outlets demonstrated that a short text message reminding patients to "Please take your malaria drugs" increased the odds of completing treatment (adjusted OR=1.45, 95% CI [1.03 to 2.04]; p= 0.028), but there was no effect on adherence of a longer text message compared to the control group [12]. The full course of treatment was completed by 61% of AL patients and 62.5% of artesunate-amodiaquine patients (61.5% overall) in the control group. Adherence was 66.4% among patients receiving the short text message and higher in patients who obtained treatment in the public sector versus the private sector. Although the impact of the text messages was not large in this study, the authors suggested that different message content might have a greater effect and should be evaluated. In Kenya, a study is currently testing the effect on adherence to AL of text messages targeted at public health facility patients (D Zurovac and A Talisuna, personal communication).

Other interventions that have been shown to increase patient adherence to antimalarials include improved packaging and a combination of community education and visual or verbal information provided to patients [41]. ACTs are already available in co-formulated blister packs, often with pictorial instructions. Package instructions for AL (e.g. Coartem®) assume that patients begin treatment in the morning, as depicted by pictures of the sun and moon for three days. Packaging could be modified to include instructions for patients who begin care later in the day, common in the private retail sector. This might depend on the importance of timely completion. On the other hand, a study in Uganda comparing the effect of different packaging found that a sticker affixed to a box of AL with the

message, “Malaria is not gone until ALL the tablets are finished” was more effective than colourful blister packs in raising the proportion of patients that completed treatment (Cohen *et al.*, in draft).

A combination of approaches is likely necessary to improve patient adherence. A study in Kenya showed that the provision of subsidised ACTs to drug shops, training of retail staff, and community awareness activities improved patient completion of treatment from 49% to 67% in household surveys [42]. Dispensers need to be appropriately trained and supervised on provision of advice on how to take ACTs, but community education or other interventions to enhance patient responsiveness to advice may also be required. Although our study did not find evidence that patients who were tested for malaria at the outlet were more likely to be adherent, a high proportion of ADDO patients did not have malaria by study RDT. Recent studies have shown that the use of RDTs in drug shops can reduce over-treatment of malaria (Visser *et al.*, under review). In Tanzania, efforts are currently underway to evaluate the use of RDTs in ADDOs (K Maloney, personal communication).

Finally, patient adherence is only one step in the pathway to treatment effectiveness and must not be considered in isolation to other health systems and individual factors [43]. Prompt access to ACTs, targeting ACTs to patients that have positive diagnostic tests, and provider compliance to test results and guidelines must also be addressed.

8.4 Conclusion

This thesis describes one of the first studies to assess patient adherence to ACTs in the private for-profit sector, where access to malaria treatment and appropriate use of ACTs must be ensured in order to reduce the burden of malaria. While adherence was suboptimal in both public and private sectors, there was some evidence of lower adherence among ADDOs, which calls for the need to better understand and support malaria treatment at drug shops. Future research priorities include developing a better understanding of the impact of care provided at outlets in both sectors on patient adherence to AL and characterising the reasons for non-adherence. These data should then support the design and

evaluation of additional interventions targeted at both dispensers and patients to improve patient adherence. Data collection tools based on self-report should be optimised and evaluated, and smart blister packs could be improved for studies that require collection of precise data on dose timing. There is also a need to clarify which components of adherence are necessary for treatment effectiveness in order to provide clear guidance to providers and patients, as well as to inform investigators assessing adherence levels and interpreting results.

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Appendices

Introduction

Appendix 1 provides examples of useful forms and tools. These include an outlet agreement form translated from Swahili (Appendix 1a), which demonstrates how dispensers were asked to participate in the studies; the registration form dispensers were asked to fill (adapted from a version on larger sized paper) (Appendix 1b); and an excerpt from the patient questionnaire showing how self-reported data on each dose were collected (Appendix 1c).

Appendix 2 contains three letters documenting ethical clearance. The first is the approval from LSHTM for the original protocol, followed by a letter approving an amendment to the protocol to allow for testing of patients with RDTs. The third letter is the approval of the revised protocol (including the amendment) from IHI.

Appendix 3 contains two components related to the text message intervention study in ADDOs. In Appendix 3a, details of the ADDO census, selection, and randomisation are presented. This is followed by the full schedule of text messages in Appendix 3b.

Appendix 1a: Outlet agreement form (English version)

Evaluation of patients treated at health facilities or drug stores in Mtwara: Invitation to participate

The Ministry of Health, Ifakara Health Institute, London School of Hygiene and Tropical Medicine and the U.S. Centers for Disease Control (CDC) are working with each other to improve malaria programs and appropriate treatment for malaria. To do this, we are conducting a research study to improve what we know about malaria treatment and how people in this region prefer to take medicine for malaria.

We would like to invite you to participate in our study without interrupting your regular treatment practices. If you agree, we would like you to record brief information about every patient whom you treat for malaria or fever in our study log for one week only. This information includes the drugs that are dispensed to the patient and details about how to find their homes, in case we want to visit them for our study.

If you do agree to participate, we will provide you with 13 packs of AL to give to patients (health facilities) or to sell yourself at the subsidized price recommended by the government (drug shops). We ask that you dispense the AL that we provide to no more than five patients per day. Our study team will be the area and will ensure that you have enough AL for each age group, but if we give you more than 13 packs, we ask that you return the extra packs at the end of the week so that we can continue our work at other outlets.

You are free to participate or not without any punishment or complaints, though we will be very happy if you do agree to participate in this study.

We will be happy to answer any questions you might have.

Do you agree to participate?

Signature: _____ _____

Date

Printed name: _____

Signature of study team member: _____ ___ _____

Date

Printed name: _____

If, at any time, you have any questions about this study, please ask the project manager (Dr. Admirabilis Kalolella, PO Box 78373, Dar es Salaam or 022-277-4714).

Appendix 1b

Outlet ID:
Outlet Name:
District:
Date:

Registration Form

For patients treated for fever or malaria

Patient Name (If attending outlet on behalf of another person, ask the name of the person who is ill)	Time (Please use Swahili time)	Patient age	Name of antimalarial drugs dispensed	If ALu dispensed, which pack?	If ALu dispensed, how many pills?	Name of head of patient's household	Village and sub-village where patient stays	Location of house where patient stays	Mobile number of patient or relative	Staff initials

Date Collected:
Collected By:

Excerpt from patient questionnaire

Note: Interview data was collected using personal digital assistants.

Questions about taking the ALu obtained at the study outlet					
Number		*The next questions will refer to the ALu that was obtained at (name of study outlet).*	*Maswali yafuatayo yatahusu ALu iliyopatikana katika (jina la kituo kinachofanyiwa utafiti).*		
158	**ALuPack**	Which blister pack of ALu was obtained at *(name of study outlet)*? 1= 1x6 (yellow) 2= 2x6 (blue) 3= 3x6 (orange) 4= 4x6 (green) 5=loose pills or incomplete pack 9=don't know	Ni aina ipi ya kifungashio cha ALu kilichopatikana (*jina la kituo kinachofanyiwa utafiti*)? 1= 1x6 (njano) 2= 2x6 (bluu) 3= 3x6 (machungwa) 4= 4x6 (kijani) 5=vidonge visivyofungashwa au kifungashio kisicho kamili 9=sijui	integer	If AluPack=5 go to Q158, otherwise go to Q159
159	**PillNum1**	Number of pills dispensed |__|__| . |__| *99.9=don't know*	Idadi ya vidonge vilivyotolewa |__|__| . |__| *99.9=don't know*	numeric	
160	**ALuCost**	How much money was paid to obtain ALu? TSH |__|__|__|__|__| 0=none, free 9=don't know	Ni kiasi gani cha pesa kilichotolewa kupata ALu? TSH |__|__|__|__|__| 0=hakuna,bure 9=sijui	numeric	
161	**DoseNum**	How many doses of ALu have been taken so far? 0=none 1=1 2=2 3=3 4=4	Umemeza/Mgonjwa amemeza dawa mara ngapi hadi muda huu? 0=hakuna 1=1 2=2 3=3 4=4	integer	If DoseNum=0 go to Q161, otherwise skip to Q163

		5=5 6=6 7=more than 6 doses 9=don't know	5=5 6=6 7=zaidi ya dozi 6 9=sijui		
162	**DoseNoneR**	Why did the patient not take any ALu? 1=forgot 2=felt better 3=gave to another person 4=saved for later use 5=was lost or stolen 6=did not understand instructions 7=patient has had adverse reaction to this medication before 8=bad taste 9=didn't know it was needed 10=took another medication 11=plan to take later 18=other	Kwa nini mgonjwa hakutumia ALu? 1=alisahau 2=alijisikia vizuri 3=alimpa mtu mwingine 4=alitunza kwa matumizi ya baadae 5=zilipotea au kuibiwa 6=hakuelewa maelekezo 7=mgonjwa alipatwa na madhara ya dawa hii awali. 8=ladha mbaya 9=hakujua zinahitajika 10=alimeza dawa zingine 11=anategemea kumeza baadae 18=ingine	Integer	If DoseNoneR=18 go to Q162, otherwise skip to Q260
163	**DoseNoneRSp**	Specify another reason the patient did not take any ALu.	Taja sababu nyingine za mgonjwa kutotumia ALu.	text	Skip to Q260
164	**GaveDose**	Who usually gave the patient his/her medication at home? 1=patient 2=mother 3=father 4=grandmother 5=grandfather	Je, kwa kawaida ni nani anayempa mgonjwa dawa nyumbani? 1=mgonjwa 2=mama 3=baba 4=bibi 5=babu	integer	

		6=aunt 7=uncle 8=sister 9=brother 10=other relative 11=other non-relative	6=shangazi, mama mdogo, mama mkubwa 7=mjomba, baba mdogo, baba mkubwa 8=dada 9=kaka 10=ndugu mwingine 11=mwingine ambaye si ndugu		
165	**Dose1Taken**	Was the first dose of ALu taken? 1=yes; 2=no; 9=don't know	Je, dozi ya kwanza ya ALu ilitumiwa? (Kila mgonjwa alimezapo dawa inahesabika kama ni dozi.) 1=ndiyo; 2=hapana; 9=sijui	integer	If Dose1Taken=1 go to Q166 , otherwise go to Q165
166	**Dose1TakenR**	Why was the first dose of ALu not taken? 1=forgot 2=felt better 3=gave to another person 4=saved for later use 5=was lost or stolen 6=did not understand instructions 7=adverse reaction to the medication 8=bad taste 9=didn't know it was needed 10=took another medication 11=plan to take later 18=other	Je, kwanini dozi ya kwanza ya ALu haikutumiwa? 1=alisahau 2=alijisikia vizuri 3=alimpa mtu mwingine 4=alitunza kwa matumizi ya baadae 5=zilipotea au kuibiwa 6=hakuelewa maelekezo 7=mgonjwa alipatwa na madhara ya dawa hii awali 8=ladha mbaya 9=hakujua zinahitajika 10=alimeza dawa zingine 11=anategemea kumeza baadae 18=ingine	integer	If Dose1TakenR=18 go to Q167, otherwise If Dose1TakenR= 7 go to Q168, otherwise go to Q169 If dose1takenR=11 then pop up msg ni kweli anategemea kumeza baadae?
	Dose1IntendTime	What time do you intend to take the first dose? 1=early morning (4am-6am)	Je, unategemea kumeza dozi ya kwanza saa ngapi? 1=alfajiri (Saa 10-12:59)	integer	

167		2=morning (7am-11:59am) 3=afternoon (12noon-3:59pm) 4=evening (4pm-6:59pm) 5=night (7pm-9:59pm) 6=late night (10pm-3:59am)	2=asubuhi (Saa 1-5:59) 3=mchana (Saa 6-9:59) 4=jioni (Saa 10-12:59) 5=usiku (Saa 1-3:59) 6=usiku sana (Saa 4-9:59)		
168	**Dose1RSp**	Specify another reason the patient did not take the first dose of Alu.	Taja sababu nyingine, kwanini mgonjwa hakutumia dozi ya kwanza ya ALu.	text	
169	**Dose1Adverse1…Dose1Adverse3**	Specify the adverse reaction to the medication.	Taja madhara ya dawa.	text	Repeat several times for multiple adverse reactions
170	**Dose1Where**	Where was the first dose taken? 1=at *(name of study outlet)* 2=at home 3=other	Je, dozi ya kwanza ilitumiwa wapi? 1=katika *(jina la kituo kinachofanyiwa utafiti)* 2=nyumbani 3=ingine	integer	
171	**Dose1Day**	How many days ago was the first dose taken? (Identify the EXACT day) |__|__| *00=today; 99=don't know*	Je, dozi ya kwanza ilitumiwa siku ngapi zilizopita (Onyesha siku HUSIKA) |__|__| *00=leo; 99=sijui*	numeric	
172	**Dose1Time**	What time was the first dose taken? 1=early morning (4am-6:59am) 2=morning (7am-11:59am) 3=afternoon (12noon-3:59pm) 4=evening (4pm-6:59pm) 5=night (7pm-9:59pm) 6=late night (10pm-3:59am)	Je, dozi ya kwanza ilitumiwa saa ngani? 1=alfajiri (Saa 10-12:59) 2=asubuhi (Saa 1-5:59) 3=mchana (Saa 6-9:59) 4=jioni (Saa 10-12:59) 5=usiku (Saa 1-3:59) 6=usiku sana (Saa 4-9:59)	integer	
173	**Dose1Pills**	How many pills were taken for the first dose? |__|__|.|__| 99.9=don't know	Je, vidonge vingapi vilitumiwa katika dozi ya kwanza? |__|__|.|__| 99.9=sijui	numeric	double entry required
174	**Dose1Meal**	Did the patient have any food or drink in the hour before taking the first dose?	Je, mgonjwa alikula au kunywa chochote saa moja kabla ya kutumia dozi ya kwanza?	integer	

		1=yes; 2=no; 9=don't know	1=ndiyo; 2=hapana; 9=sijui		
175	**Dose1MealType**	Which type of food or drink did the patient have? 1=food without oil (fruits, ugali or rice cooked without oil) 2=food with oil (peanuts, cashews, avocado, foods cooked with oil, meat, fish, etc.) 3=milk 4=water 5=soda 6=chai 8=other 9=don't know	Ni aina gani ya chakula au kinywaji mgojwa amepata? 1=chakula kisicho na mafuta (matunda, ugali au wali uliopikwa bila mafuta) 2=chakula chenye mafuta (karanga, korosho, parachichi, chakula kilichopikwa na mafuta, nyama, samaki, n.k.) 3=maziwa 4=maji 5=soda 6=chai 8=ingine 9=sijui	check box	If Dose1MealType=8 go to Q175, otherwise continue with Q176
176	**Dose1MealSp**	Specify other food or drink that was taken with the first dose.	Taja chakula au kinywaji kingine ambacho kilitumiwa pamoja na dozi ya kwanza.	text	
177	**Dose1Vomit**	Did the patient vomit within 30 minutes of taking the first dose of the medication? 1=yes; 2=no; 9=don't know	Je, mgonjwa alitapika ndani ya dakika 30 baada ya kutumia dozi ya kwanza ya dawa? 1=ndio; 2=hapana; 9=sijui	integer	If Dose1Vomit=1 go to Q178, otherwise go to Q177
178	**Dose1VRedose**	Did the patient take a replacement dose of the medication after vomiting the first dose? 1=yes; 2=no; 9=don't know	Je, mgonjwa alirudia dozi ya dawa baada ya kutapika dozi ya kwanza? 1=ndio; 2=hapana; 9=sijui	integer	

Questionnaire continues with Doses 2-6, as in Q165-178.

Appendix 2: Ethical clearances

(Approval letters on next page)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Katia Bruxvoort
Research Degree Student
DCd/ITD
LSHTM

15 June 2012

Dear Ms Bruxvoort,

Study Title: **Evaluation of patient adherence to Artemether lumefantrine obtained from public and private drug outlets in Tanzania**
LSHTM ethics ref: **6205**

Thank you for your application of 15 May 2012 for the above research, which has now been considered by the Interventions Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

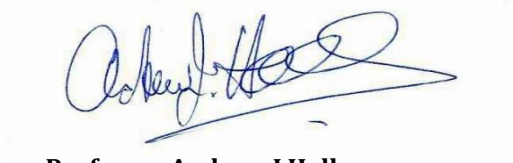
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM ethics application	n/a	14/05/2012
Protocol	V001	14/05/2012
Information Sheet		14/05/2012
Consent form		14/05/2012

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form. All studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. An annual report form (form E3) is required on the anniversary of the approval of the study and should be submitted during the lifetime of the study. At the end of the study, please notify the committee via form E5.

Yours sincerely,



Professor Andrew J Hall
Chair
ethics@lshtm.ac.uk
http://intra.lshtm.ac.uk/management/committees/ethics/

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Katia Bruxvoort
Research Degree Student
DCD/ITD
LSHTM

24 July 2012

Dear Dr Bruxvoort,

Study Title:	**Evaluation of patient adherence to Artemether lumefantrine obtained from public and private drug outlets in Tanzania**
LSHTM ethics ref:	**6205**
LSHTM amend no:	**A346**

Thank you for your application of 29 June 2012 for the amendment above to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Interventions Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM amendment application	n/a	29/06/2012
Protocol	V2	29/06/2012

After ethical review

Any further changes to the application must be submitted to the Committee via an E2 amendment form. The Principal Investigator is reminded that all studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. An annual report form (form E3) is required on the anniversary of the approval of the study and should be submitted during the lifetime of the study. At the end of the study, please notify the committee via form E5.

Yours sincerely,

Professor Andrew J Hall
Chair
ethics@lshtm.ac.uk
http://intra.lshtm.ac.uk/management/committees/ethics/

IFAKARA HEALTH INSTITUTE
research | training | services

INSTITUTIONAL REVIEW BOARD

P O BOX 78373 DAR ES SALAAM, TANZANIA

Tel +255 (0) 22 2774714, Fax: + 255 (0) 22 2771714 Email: irb@ihi.or.tz

FEEDBACK FORM TO THE PRINCIPLE INVESTATORS/RESEARCHERS ON PROTOCOL SUBMISSION

1	Proposal Title	**IMPACT 2: EVALUATION OF PATIENT ADHERANCE TO ARTEMETHER-LUMEFANTRINE OBTAINED FROM PUBLIC AND PRIVATE DRUG OUTLETS IN TANZANIA**
2	Identification numbers (versions numbers/dates) of the documents reviewed	
3	The name and title of the applicant	**PI: AB KALOLELA**
4	The name of the site(s)	**Ifakara**
5	The date and the place of the decision	**5th June 2012, IHI Offices , DAR ES SALAAM**
6	The name of the EC taking the decision	**IHI- IRB**
7	A clear statement of the decision reached	**APPROVED (Certificate being prepared)**

NOTE

To facilitate the quick review by the IRB members you are advised to bring the required advice information within one week after receiving this feedback

Signature of IRB Secretary: _____

Appendix 3a: ADDO sampling and randomisation methods

ADDO census. A census of all ADDOs in Mtwara Region was conducted to identify location (GPS coordinates and time to reach by car from the district headquarters), antimalarials in stock and the number of each antimalarial sold in the previous seven days, and mobile phone use of each dispenser. In addition, information was collected on ADDO ownership (name of owner and other ADDOs owned), whether dispensers work at any other ADDOs and names of these ADDOs , whether any close relatives ("ndugu wa karibu") work at any other ADDOs and names of these ADDOs, and dispenser age, education, health-related qualifications, and malaria-containing trainings received in previous five years. Dispensers were also asked about the number of people working in other ADDOs with whom they communicate, location of these ADDOs, and frequency of communication. Finally, dates of registration and accreditation were recorded.[1]

Preparation of sampling frame. Of the 156 ADDOs censused, two were removed from the sampling frame due to location on the Mozambique border (with potential for customers to live on either side), one was in a prison area, one refused to complete the census, and one ADDO was censused twice. The remaining 151 ADDOs were then checked against the following exclusion criteria.

i. More than 60 minutes by study car required to arrive at ADDO from district headquarters- This was very subjective, as study teams conducting the census did not always come from the district headquarters. Comparison with other sources of data (e.g. Google Earth and the IHI Mtwara team) was necessary to determine the time required to reach each ADDO. Since only one of the 151 ADDOs was located more than 60 minutes away (at 75 minutes), the maximum time for reaching each ADDO was increased to 75 minutes. Thus, no ADDOs were excluded based on this criterion.

[1] Data on outlet and dispenser characteristics presented in Chapter 5 are based on the later dispenser interviews and not on the ADDO census.

ii. Sold less than five ACTs in the previous week- 14 ADDOs. Half of these shops had ACTs in stock and half did not. These 14 ADDOs were removed from the sampling frame.

iii. At least one dispenser working at the ADDO did not use a mobile phone number- six ADDOs were removed from the sampling frame.

The final sampling frame contained 131 ADDOs.

Sampling procedure. The following steps were followed to conduct the sampling:

i. Assign a random number in Stata to each ADDO.

ii. Sort ADDOs by random number, and copy list to Excel.

iii. Select the ADDO at the top of the list, beginning with the first random number.

iv. See if dispensers working at the ADDO work at any other ADDOs or if any other ADDOs have the same owner. If so, remove these other ADDOs from the sampling frame by deleting on Excel list and dropping from Stata.

v. Use Stata geonear command to calculate the distance between each ADDO.

vi. Check if the selected ADDO has any other ADDOs within 500 meters. If so, remove these other ADDOs from the sampling frame by deleting on Excel list and dropping from the original Stata data file (not with all the distance matrix variables generated by geonear).

vii. Save the Stata data file with a new name.

viii. Go back to step iii, selecting the next ADDO on the list. Repeat steps iii-viii, each time recalculating the distance matrix and saving with a new name.

ix. Continue until 78-80 ADDOs are selected.

Sampling results. Conducting this manual sampling process was very time consuming, with the first round taking nearly six hours. Upon completion, exactly 72 ADDOs had been selected. This was not sufficient, as 6-10 alternates were desired in case of ADDO closings or refusal to participate. Thus, the sampling was repeated by relaxing the criteria as follows:

i. ADDOs were excluded if they sold less than five antimalarial drugs instead of less than five ACTs. This added seven more shops to the sampling frame.

ii. The minimum distance between shops was reduced to 400 meters.

The second round of sampling resulted in 83 ADDOs. Of these, 57 were in peri-urban wards, 25 were in rural wards, and one did not have rural or urban defined and was inadvertently dropped, leaving 82 selected ADDOs. Had this second round or subsequent rounds not resulted in 72-80 ADDOs, I would have relaxed several criteria each time prior to repeating the sampling.

Randomisation. While ADDOs were stratified by location in peri-urban or rural wards, restricted randomisation was not used. The main reason for this decision was that the number of randomisation units was large, increasing the chances of a reasonably balanced sample. Secondly, perfect balance on other variables, such as dispenser education and health-related qualifications or number of customers purchasing antimalarial drugs per day, was not thought to be essential, as the effect of these characteristics on dispenser advice is unclear. Thus, from the 82 selected ADDOs, the intervention was randomly allocated to 29 of the 57 urban ADDOs and 13 of the 25 rural ADDOs. The last three urban and rural intervention ADDOs and the last two urban and rural control ADDOs were designated as alternates, for a final count of 36 intervention, 36 control, and 10 alternate ADOOs. In practice, alternates were enrolled in the study to boost sample sizes, as overall patient registration was lower than expected.

Appendix 3b: Schedule of text messages

Week 1

Day 1

Introduction message (send separately) (179 characters):

Aksante kwa kusoma ujumbe huu, kuanzia sasa tutakutumia ujumbe mfupi wa maandishi kila siku kwa muda wa miezi miwili. Jishindie muda wa maongezi kwa kujibu maswali yatakayoulizwa.

Content message (1): **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.**

Complementary component: "*Kauli njema haikusaidii wewe kupata faida pekee bali inakusaidia kujifunza vitu vipya kila siku."*

MSG (147 characters):

> **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.** "*Kauli njema haikusaidii kupata faida tu bali kujifunza vitu vipya kila siku."*

Day 2

Content message (2): **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2.**

Complementary component: *Siri pekee yakufanya kazi vizuri nikua na mudi yakufanya kazi.*

MSG (177 characters):

> **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2.** "*Siri pekee ya kufanya kazi vizuri ni kuwa na mudi yakufanya kazi."*

Day 3

Content message (3): **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.**

Complementary component: *Si kila kinachohesabika kinafaa.*

MSG (99 characters) :

> **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.** "*Si kila kinachohesabika kinafaa."*

Day 4

Content message (4): **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.**

Complementary component: "*Daima huonekana haiwezekani hadi itakapofanyika!"*

MSG (135 characters):

> **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozinyingine.** *"Daima huonekana haiwezekani hadi itakapofanyika!"*

Day 5

Content message (5): **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.**

Complementary component: "*Kama huwezi kufanya mambo makubwa fanya madogo kwa ufanisi zaidi."*

MSG (169 characters):

Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote. *"Kama huwezi kufanya mambo makubwa fanya madogo kwa ufanisi zaidi."*

Week 2

Day 1

Content message (6): **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.**

Complementary component: "*Afya sio tu kukosekana kwa maradhi*."

MSG (144 characters) :

Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria." *Afya sio tu kukosekana kwa maradhi*."

Day 2

Content message (7): **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu, yakitokea aendelee na matibabu.**

Complementary component: "*Afya ndiyo mali halisi sio vipande vya dhahabu na shaba."*

MSG (158 characters):

Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu. "*Afya ndiyo mali halisi sio vipande vya dhahabu na shaba."*

MSG (133 characters) (send separately)**:**

Madhara madogo madogo yatokanayo na Alu ni kama kizunguzungu, kichefuchefu, kikohozi, kuumwa kichwa, kuumwa tumbo na uchovu wa mwili.

Day 3

Content message (3): **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.**

Complementary component: "*Dozi ya 2 ya dawa mseto ya malaria inatakiwa imezwe baada ya masaa mangapi? Jibu kwenda 0784666714"*

MSG (165 characters):

Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta. *"Dozi ya 2 ya dawa mseto ya malaria inatakiwa imezwe baada ya masaa mangapi? Jibu kwenda 0784666714"*

Day 4

Content message (2): **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2.**

Complementary component: "*Kawaida ni kama sheria."*

MSG (135 characters):

Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2. "*Kawaida ni kama sheria."*

Day 5

Content message (1): **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.**

Complementary component: "*Ugumu wa maisha usikukwaze,kwani hakuna awezaye kuzuia matatizo."*

MSG (136 characters):

> **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.** "*Ugumu wa maisha usikukwaze, kwani hakuna awezaye kuzuia matatizo."*

Week 3

Day 1

Content message (4): **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.**

Complementary component: "*Kujiwekea malengo ni hatua ya kwanza ya mafanikio."*

MSG (138 characters):

> **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.** "*Kujiwekea malengo ni hatua ya kwanza ya mafanikio."*

Day 2

Content message (5): **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.**

Complementary component: "*Jina jema hungara gizani*."

MSG(128 characters):

> **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.** "*Jina jema hungara gizani."*

Day 3

Content message (6): **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.**

Complementary component: "*Je, mgonjwa akitapika dakika tano baada ya kumeza dawa ila vidonge havionekani anatakiwa afanyeje? Jibu kwenda 0784666714"*

MSG (230 characters):

> **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.** "*Je, mgonjwa akitapika dakika tano baada ya kumeza dawa ila vidonge havionekani anatakiwa afanyeje? Jibu kwenda 0784666714"*

Day 4

Content message (1): **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.**

Complementary component: "*Je, kama mgonjwa atameza dozi ya kwanza ya dawa mseto saa nne usiku, dozi ya pili itamezwa saa ngapi? Jibu kwenda 0784666714"*

MSG (195 characters):

> **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.** "*Je, kama mgonjwa atameza dozi ya kwanza ya dawa mseto saa nne usiku, dozi ya pili itamezwa saa ngapi? Jibu kwenda 0784666714"*

Day 5

Content message (7): **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu.**

Complementary component: "*Huwezi kuvuka bahari isipokuwa kama unauwezo wa kutokuona mwambao."*

MSG (168 characters):

> **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu.** "*Huwezi kuvuka bahari isipokuwa kama unauwezo wa kutokuona mwambao."*

Week 4

Day 1

Content message (2): **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2.**

Complementary component: "*Ukiamini jambo lolote, amini hivyo pasipo kusita hata kidogo."*

MSG (173characters):

> **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2.** "*Ukiamini jambo lolote, amini hivyo pasipo kusita hata kidogo."*

Day 2

Content message (4): **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.**

Complementary component: "*Kabla yakuongea jiulize, ni muhimu? Ni kweli? Ni zaidi ya kukaa kimya?"*

MSG (157 characters):

> **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita arudie kumeza dozi nyingine.** "*Kabla yakuongea jiulize ni muhimu? Ni kweli? Ni zaidi ya kukaa kimya?"*

Day 3

Content message (3): **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.**

Complementary component: "*Alu inapaswa kumezwa na chakula cha aina gani? Jibu kwenda 0784666714"*

MSG (136 characters):

> **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.** "Alu inapaswa kumezwa na chakula cha aina gani? *Jibu kwenda 0784666714"*

Day 4

Content message (5): **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.**

Complementary component: "*Je, mgonjwa akitapika dakika ishirini na tano baada ya kumeza dawa anatakiwa afanyeje? Jibu kwenda 0784666714"*

MSG (212 characters):

Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote. "*Je, mgonjwa akitapika dakika ishirini na tano baada ya kumeza dawa anatakiwa afanyeje? Jibu kwenda 0784666714"*

Day 5

Content message (7): **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu.**

Complementary component: "*Daima tunafikili jinsi ya kuwabadilisha wenzetu lakini hatufikilii jinsi ya kubadilika mienendo yetu wenyewe."*

MSG (211 characters):

Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu. "*Daima tunafikili jinsi ya kuwabadilisha wenzetu lakini hatufikilii jinsi ya kubadilika mienendo yetu wenyewe."*

Week 5

Day 1

Content message (6): **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.**

Complementary component: "*Mlango mmoja ukifungwa, mwingine hufunguka iwapo umejishughulisha."*

MSG (175 characters):

Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria. "*Mlango mmoja ukifungwa, mwingine hufunguka iwapo umejishughulisha."*

Day 2

Content message (1): **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.**

Complementary component: "*Ni sahihi mgonjwa kumeza dawa mseto akiwa hajala chakula? Jibu kwenda 0784666714"*

MSG (151 characters):

Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa. "*Ni sahihi mgonjwa kumeza dawa mseto akiwa hajala chakula? Jibu kwenda 0784666714"*

Day 3

Content message (5): **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.**

Complementary component: "*Vitu havibadiliki, watu ndio wanobadilika."*

MSG (146 characters):

Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote. "*Vitu havibadiliki, watu ndio wanobadilika."*

Week 6

Day 1

Content message (2): **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili; halafu ameze dawa kila baada ya masaa 12 kwa siku 2.**

Complementary component: *"Dozi ya kwanza ya dawa mseto inatakiwa imezwe chini ya uangalizi wa nani? Jibu kwenda 0784666714"*

MSG (210 characters):

Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili; halafu ameze dawa kila baada ya masaa 12 kwa siku 2. *"Dozi ya kwanza ya dawa mseto inatakiwa imezwe chini ya uangalizi wa nani? Jibu kwenda 0784666714"*

Day 2

Content message (4): **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.**

Complementary component: "*Utajiri sio kipimo cha afya."*

MSG (116 characters):

> **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.** *"Utajiri sio kipimo cha afya."*

Day 3

Content message (6): **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.**

Complementary component: "*Mafanikio mazuri huja baada ya mahangaiko."*

MSG (151 characters):

> **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.** "*Mafanikio mazuri huja baada ya mahangaiko."*

Week 7

Day 1

Content message (3): **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.**

Complementary component: "*Kila mlango na ufunguo wake."*

MSG (95 characters):

> **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta. "***Kila mlango na ufunguo wake."*

Day 2

Content message (1): **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.**

Complementary component: "*Mwenye kusita hupoteza."*

MSG (94 characters):

> **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.** "*Mwenye kusita hupoteza."*

Day 3

Content message (7): **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu, yakitokea aendelee na matibabu.**

Complementary component: "*Watoto wenye kilo5 hadi 15 wanameza vidonge vingapi vya dawa mseto ya malaria? Jibu kwenda 0784666714"*

MSG (204 characters):

> **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu, yakitokea aendelee na matibabu.** "*Watoto wenye kilo5 hadi 15 wanameza vidonge vingapi vya dawa mseto ya malaria? Jibu kwenda 0784666714"*

Week 8

Day 1

Content message (6): **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.**

Complementary component*: "Amini kwa moyo wako utakifanya ulichopaswa kufanya."*

MSG (160 characters):

> **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.** "*Amini kwa moyo wako utakifanya ulichopaswa kufanya."*

Day 2

Content message (5): **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.**

Complementary component*: "Baada ya dozi ya pili, dozi zingine za dawa mseto humezwa kila baada ya masaa mangapi? Jibu kwenda 0784666714"*

MSG (213 characters):

> **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.** "*Baada ya dozi ya pili, dozi zingine za dawa mseto humezwa kila baada ya masaa mangapi? Jibu kwenda 0784666714"*

Day 3

Content message (4): **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.**

Complementary component: "*Dozi ya kwanza ya dawa mseto inatakiwa imezwe chini ya uangalizi wa nani? Jibu kwenda 0784666714"*

MSG (183 characters):

Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine "*Dozi ya kwanza ya dawa mseto inatakiwa imezwe chini ya uangalizi wa nani? Jibu kwenda 0784666714"*

Week 9

Day 1

Content message (7): **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu.**

Complementary component: "*Kujua haitoshi; ni lazima kufanya. Nia haitoshi; ni lazima kutenda."*
MSG (169 characters):

Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu. "*Kujua haitoshi; ni lazima kufanya. Nia haitoshi; ni lazima kutenda."*

Day 2

Content message (1): **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.**
Complementary component: "*Mafanikio katika maisha, au kitu, yanategemeana na idadi ya watu unashirikiana nao."*

MSG (154 characters):

Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa. "*Mafanikio katika maisha, au kitu, yanategemeana na idadi ya watu unashirikiana nao."*

Day 3

Content message (2): **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2.**
Complementary component: "*Mgonjwa afanye nini ili kumaliza vimelea vyote vya malaria? Jibu kwenda 0784666714"*
MSG (194 characters):

Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2. "*Mgonjwa afanye nini ili kumaliza vimelea vyote vya malaria? Jibu kwenda 0784666714"*

Week 10

Day 1

Content message (4): **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.**
Complementary component: "*Furaha katika maisha yako inategemea na ubora wa mawazo yako; kwahiyo waza ipasavyo".*
MSG (172 characters):

Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine. "*Furaha katika maisha yako inategemea na ubora wa mawazo yako; kwahiyo waza ipasavyo."*

Day 2

Content message (3): **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.**
Complementary component: "*Watu wenye kutaka kujua mengi, huishi sio muda mrefu tu bali kwa furaha pia."*
MSG (143 characters):

Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta. "*Watu wenye kutaka kujua mengi, huishi sio muda mrefu tu bali kwa furaha pia."*

Day 3

Content message (5): **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.**
Complementary component: "*Dawa mseto ya malaria humezwa kwa siku ngapi? Jibu kwenda 0784666714"*
MSG (172 characters):

> **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.** "*Dawa mseto ya malaria humezwa kwa siku ngapi? Jibu kwenda 0784666714"*

Week 11
Day 1
Content message (1): **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.**
Complementary component: "*Furaha haikai katika vitu tunavyomiliki au katika dhahabu, bali hukaa moyoni."*
MSG (148 characters):

> **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.** "*Furaha haikai katika vitu tunavyomiliki au katika dhahabu, bali hukaa moyoni."*

Day 2
Content message (6): **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.**
Complementary component: *Watoto wenye kilo5 hadi 15 wanameza vidonge vingapi vya dawa mseto ya malaria? Jibu kwenda 0784666714*
MSG (209 characters):

> **Mshauri mgonjwa kumaliza matibabuhata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.** "*Watoto wenye kilo5 hadi 15 wanameza vidonge vingapi vya dawa mseto ya malaria? Jibu kwenda 0784666714"*

Day 3
Content message (7): **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu.**
Complementary component: Ni vema uwe mtu wa thamani sio mtu wa mafanikio.
MSG (150 characters):

> **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu yakitokea aendelee na matibabu.** "Ni vema uwe mtu wa thamani sio mtu wa mafanikio."

Week 12
Day 1
Content message (3): **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.**
Complementary component*: "Mafanikio katika maisha ni kuweza kuishi upendavyo."*
MSG (118 characters):

> **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.** *"Mafanikio katika maisha ni kuweza kuishi upendavyo."*

Day 2

Content message (4): **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.**

Complementary component: "*Siri ya mafanikio ni kufahamu kitu ambacho hamna mtu anayejua."*

MSG (150 characters):

> **Mwambie mgonjwa kama akitapika kabla ya nusu saa kupita, arudie kumeza dozi nyingine.** "*Siri ya mafanikio ni kufahamu kitu ambacho hamna mtu anayejua."*

Day 3

Content message (2): **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2**.

Complementary component: "*Taja mojawapo ya madhara madogo madogo yatokanayo na dawa mseto ya malaria. Jibu kwenda 0784666714"*

MSG (211 characters):

> **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2**. "*Taja mojawapo ya madhara madogo madogo yatokanayo na dawa mseto ya malaria. Jibu kwenda 0784666714."*

Week 13

Day 1

Content message (5): **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.**

Complementary component: "*Ni ujinga kuogopa kitu ambacho uwezi kukizuia."*

MSG (150 characters):

> **Mshauri mgonjwa kumaliza vidonge VYOTE kwa siku 3 kama ulivyomuelekeza ndiko kutamaliza malaria yote.** *"Ni ujinga kuogopa kitu ambacho uwezi kukizuia."*

Day 2

Content message (6): **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.**

Complementary component: "*Je, mtoto wa chini ya kilo tano atameza vidonge vingapi vya dawa mseto ya malaria? Jibu kwenda 0784666714"*

MSG (214 characters):

> **Mshauri mgonjwa kumaliza matibabu hata kama atajisikia nafuu ilikumaliza kabisa vimelea vyote vya malaria.** "*Je, mtoto wa chini ya kilo tano atameza vidonge vingapi vya dawa mseto ya malaria? Jibu kwenda 0784666714"*

Day 3

Content message (7): **Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu, yakitokea aendelee na matibabu.**

Complementary component: "*Hakuna kushindwa isipokuwa katika kutokujaribu tena."*

MSG (155 characters):

Mwambie mgonjwa madhara madogo madogo yatokanayo na matibabu ya Alu, yakitokea aendelee na matibabu. "*Hakuna kushindwa isipokuwa katika kutokujaribu tena.*"

Week 14

Day 1

Content message (3): **Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta.**

Complementary component: "*Njia ya pekee ya kuandaa maisha ni kuanza kuishi.*"

MSG (116 characters):

Mueleze mgonjwa kuwa ALu imezwe pamoja na chakula chenye mafuta. "*Njia ya pekee ya kuandaa maisha ni kuanza kuishi.*"

Day 2

Content message (2): **Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili halafu ameze dawa kila baada ya masaa 12 kwa siku 2.**

Complementary component: "*Napenda ndoto za maisha ya jayo kuliko simuliza ya yaliyopita.*"

MSG (175 characters):

Mshauri mgonjwa kumeza dozi ya 2 baada ya masaa 8 kamili; halafu ameze dawa kila baada ya masaa 12 kwa siku 2. "*Napenda ndoto za maisha ya jayo kuliko simuliza ya yaliyopita.*"

Day 3

Content message (1): **Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa.**

Complementary component: "*Je, mgonjwa akitapika dakika arobaini baada ya kumeza dawa mseto atapaswa kurudia dozi hiyo? Jibu kwenda 0784666714?*"

MSG (185 characters):

Hakikisha dozi ya 1 ya ALu imemezwa chini ya uangalizi wa Mtoa Dawa "*Je, mgonjwa akitapika dakika arobaini baada ya kumeza dawa mseto atapaswa kurudia dozi hiyo? Jibu kwenda 0784666714*"